

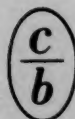
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THE INFLUENCE OF CERTAIN SUBSTANCES ON THE SOLUBILITY OF BENZOIC ACID IN ETHYL ALCOHOL AND 50% AQUEOUS ETHYL ALCOHOL

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The influence of various electrolytes on the solubility of benzoic acid in aqueous solutions has been investigated by a large number of authors [1-18], but only in the work of Bockris and co-workers [10-18] has the solubility of benzoic acid in aqueous-alcoholic, aqueous dioxane, and aqueous ethylene glycol solutions with the addition of certain salts been studied.

We set ourselves the task of studying the action of lithium chloride, lithium perchlorate, phenanthrene, biphenyl, diphenylamine, resorcinol, and urea on the solubility of benzoic acid in ethyl alcohol and also the influence of lithium chloride and perchlorate on the solubility of benzoic acid in 50% ethyl alcohol.

EXPERIMENTAL

The solubility was determined by the method described earlier [17]. The benzoic acid, after repeated recrystallization from water, had m.p. 121.9°. The other substances after appropriate purification had melting points close to those given in the literature. The salts were purified by crystallization from water and were dehydrated to constant weight.

Table 1 gives the results of the determination of the solubility of benzoic acid in solutions of the substance and the salting-out constants. All the substances added, with the exception of urea, diminished the solubility of benzoic acid in alcohol.

TABLE 1.

Substance added	C	S _{35°}	S _{45°}	K _{35°} *	K _{45°} *
Phenanthrene	0.1	0.155	0.188	1.34	1.29
Diphenyl	0.125	0.176	0.211	0.630	0.630
Resorcinol	1.0	0.188	0.227	0.049	0.046
Diphenylamine	0.25	0.207	0.247	0.033	0.041
Urea	0.5	0.225	0.264	-0.056	-0.035
LiCl	1.0	0.171	0.208	0.091	0.084
LiClO ₄	1.0	0.159	0.196	0.123	0.113

* K represents the salting-out constants, determined by Sechenov's equation

$$\log \frac{S_0}{S} = KC, \text{ where } S_0 \text{ is the solubility of } C_6H_5COOH \text{ in the pure solvent.}$$

Phenanthrene and biphenyl possessed the largest salting-out effect and diphenylamine the smallest. Urea increased the solubility of benzoic acid both in water and, though to a smaller degree, in alcohol.

TABLE 2. Solubility of Benzoic Acid in Solutions of Lithium Chloride and Perchlorate

Salt conc.	S_{35°	S_{45°	$\lg_{35^\circ} \frac{S_0}{S}$	$\lg_{45^\circ} \frac{S_0}{S}$	$K_{35^\circ}^*$	$K_{45^\circ}^*$
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$C_6H_5COOH-C_2H_5OH-LiCl$

0	0.211	0.253				
0.25	0.196	0.239	0.0288	0.0247	0.115	0.094
0.5	0.188	0.227	0.0455	0.0461	0.100	0.092
0.75	0.178	0.218	0.0647	0.0936	0.094	0.086
1.0	0.171	0.208	0.0990	0.0892	0.091	0.084
1.5	0.159	0.197	0.1215	0.1086	0.081	0.072
2.0	0.157	0.195	0.1284	0.1131	0.064	0.056
2.25	0.161	0.196	0.1177	0.1097	0.052	0.049
2.5	0.164	0.199	0.1090	0.1031	0.044	0.041

$C_6H_5COOH-(C_2H_5OH\ 50\% + H_2O\ 50\%)-LiCl$

0	0.062	0.092				
0.25	0.057	0.084	0.0465	0.0395	0.186	0.158
0.5	0.052	0.0785	0.0764	0.0717	0.153	0.143
1.25	0.045	0.067	0.1392	0.1377	0.139	0.138
1.5	0.040	0.061	0.1893	0.1785	0.126	0.119
2.0	0.0355	0.054	0.2422	0.2315	0.121	0.116

$C_6H_5COOH-C_2H_5OH-LiClO_4$

0	0.211	0.253				
1.0	0.159	0.196	0.1229	0.1131	0.123	0.113
1.25	0.150	0.184	0.1482	0.1383	0.118	0.110
2.0	0.138	0.172	0.1854	0.1689	0.0927	0.0844

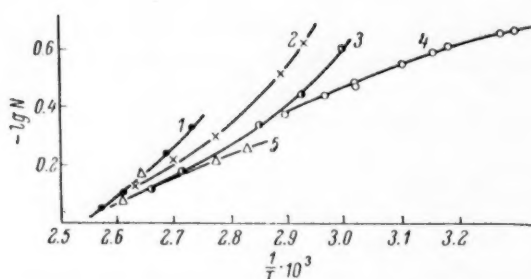


Fig. 1. $\lg N$ as a function of $1/T$. Solubility of benzoic acid in: 1) resorcinol, 2) diphenylamine, 3) biphenyl, 4) alcohol, 5) urea.

If, to explain this effect of the added substances on the solubility of benzoic acid in alcohol, the solubility of benzoic acid in biphenyl, resorcinol, diphenylamine, and urea is compared with its solubility in alcohol (Fig. 1 gives the dependence of $\lg N$ on $1/T$, where N is the molar fraction of benzoic acid), it can be seen that alcohol dissolves benzoic acid better than biphenyl, diphenylamine, and resorcinol. Hence, the addition of these substances to alcohol must lead to a diminution in the solubility of benzoic acid, i.e. to its salting-out. The solubility of benzoic acid in urea, as can be seen from Fig. 1, is somewhat higher than in alcohol. Hence, urea causes a slight salting-in of benzoic acid. With regard to lithium chloride and perchlorate, they do not dissolve benzoic acid at all and must, therefore, salt it out from any solvent.

We further studied the influence of the concentration of lithium chloride on the solubility of benzoic acid in alcohol and 50% aqueous alcohol, and the influence of the concentration of lithium perchlorate on the solubility of benzoic acid in alcohol. The experimental results are given in Table 2 and Fig. 2 in the form of the relation of $\lg \frac{S_0}{S}$ to the concentration of the salt in the solution (C). For comparison, the values calculated by us from Larsson's data [3] of $\lg \frac{S_0}{S}$ for the system $C_6H_5COOH-H_2O-LiCl$ are also plotted in Fig. 2. Fig. 2 shows that lithium chloride salts out benzoic acid most strongly from water, then from 50% alcohol, and least from alcohol. The ratio of $\lg \frac{S_0}{S}$ in water to that in 50% alcohol rises with an increase in the concentration of the electrolyte. The values of $\lg \frac{S_0}{S}$ in relation to the concentration of lithium perchlorate shows similar changes, but lithium perchlorate salts out benzoic acid from alcohol more strongly than lithium chloride.

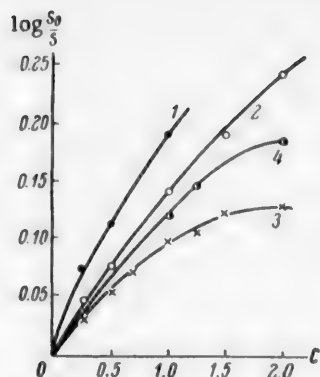


Fig. 2. $\log \frac{S_0}{S}$ as a function of C . 1) system $C_6H_5COOH-H_2O-LiCl$ (according to the data of [3]), 2) system $C_6H_5COOH-(50\% C_2H_5OH - 50\% H_2O)-LiCl$, 3) system $C_6H_5COOH-C_2H_5OH-LiCl$, 4) system $C_6H_5COOH-C_2H_5OH-LiClO_4$.

SUMMARY

1. The influence of lithium chloride and lithium perchlorate, biphenyl, diphenylamine, phenanthrene, resorcinol, and urea on the solubility of benzoic acid in ethyl alcohol has been studied.

2. Lithium chloride and perchlorate, biphenyl, diphenylamine, phenanthrene, and resorcinol diminish the solubility of benzoic acid; urea increases it.

3. The dependence of the salting-out constants on the concentration of lithium chloride in anhydrous and 50% alcohol has been studied.

With an increase in the concentration of the electrolyte, the salting-out constant diminishes.

4. Lithium chloride salts out benzoic acid most strongly from water, then from 50% alcohol, and least from anhydrous alcohol.

5. The influence of the concentration of lithium perchlorate on the solubility of benzoic acid in alcohol has been studied. The salting-out constant diminishes with an increase in the concentration of the salt.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

THE INFLUENCE OF CERTAIN SUBSTANCES ON THE SOLUBILITY OF NAPHTHALENE IN METHYL ALCOHOL

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The influence of salts on the solubility of non-electrolytes has been studied mainly in aqueous solutions and only a small number of investigations has been devoted to the study of this phenomenon in other solvents [1-8]. The present paper gives the results of a study of the influence of sodium bromide and iodide, lithium chloride and perchlorate, ethylpyridinium iodide, phenanthrene, biphenyl, diphenylamine, resorcinol, and urea on the solubility of naphthalene in methyl alcohol.

EXPERIMENTAL

After repeated purification, the substances had the following melting points: phenanthrene, 99.4°; biphenyl, 69.0°; diphenylamine, 52.6°; urea, 132.6°; resorcinol, 109.5°; and naphthalene, 79.8°.

The salts were purified by the recrystallation from water and were dehydrated at appropriate temperatures to constant weight. The methyl alcohol, after dehydration, had d_4^{20} 0.7920 and n_D 1.3288.

The solubility was determined by the method described in a previous communication [8].

The table gives the results of the two determinations of the solubility of naphthalene in methyl alcohol with the addition of the substances mentioned above at 35 and 45°.

Substance	C	S		K	
		35°	45°	35°	45°
—	0	0.0360	0.0550		
NaI	0.1	0.0330	0.0515	0.377	0.285
NaBr	0.1	0.0330	0.0500	0.377	0.413
LiCl	0.1	0.0345	0.0515	0.185	0.285
LiClO ₄	0.1	0.0354	0.0535	0.073	0.120
C ₅ H ₅ N · C ₂ H ₅ I	0.1	0.0373	0.0563	-0.155	-0.102
(C ₆ H ₅) ₂	0.1	0.0405	0.0601	-0.512	-0.386
(C ₆ H ₅) ₂ NH	0.1	0.0395	0.0585	-0.403	-0.268
(C ₆ H ₄ CH) ₂	0.1	0.0405	0.0605	-0.512	-0.414
C ₆ H ₄ (OH) ₂	2.0	0.0350	0.0525	0.006	0.0106
(NH ₂) ₂ CO	1.0	0.0320	0.0470	0.051	0.068

The solubility N is expressed in molar fractions.

The salting-out constant was calculated from I. Sechenov's equation

$$\log \frac{S_0}{S} = KC,$$

where: S_0 is the solubility of naphthalene in methyl alcohol, S is the solubility of naphthalene in a solution of the given substance, the concentration of which is C.

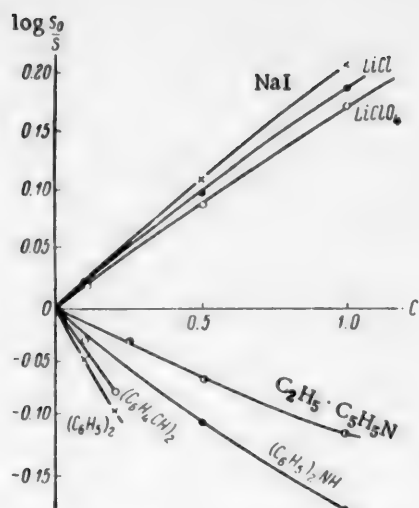


Fig. 1. $\log \frac{S_0}{S}$ as a function of C . Explanation in the text.

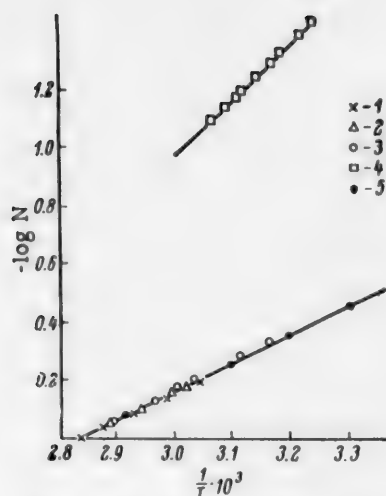


Fig. 2. $\log N$ as a function of $1/T$. Solubility of naphthalene in: 1) biphenyl, 2) phenanthrene, 3) diphenylamine, 4) methyl alcohol, 5) ideal straight line.

Fig. 1 gives $\log S_0/S$ as a function of the concentration of the added substance. As can be seen from the data of the Table and Fig. 1, sodium iodide and bromide and lithium chloride and perchlorate diminish the solubility of naphthalene in methyl alcohol; resorcinol and urea do not affect the solubility in small concentrations but have a salting-out action at high concentrations.

The salting-out action is explained by the fact that sodium iodide and bromide and lithium chloride and perchlorate do not dissolve naphthalene. As our experiments have shown, the addition of them to naphthalene causes no change in the melting point of the naphthalene.

In the fusibility diagram for the resorcinol-naphthalene system [9], the liquidus curve of naphthalene has a very gently sloping portion of great extent, which indicates the tendency of this system to separate. A eutectic is found at 76° and a content of resorcinol of 4%.

Biphenyl, phenanthrene, diphenylamine, and ethylpyridinium iodide increase the solubility of naphthalene in methyl alcohol. In Fig. 2 we have plotted the values of the ideal solubility of naphthalene, calculated from I. Schroeder's equation, with the coordinates $\log N$ against $1/T$, and the values of the solubilities of naphthalene in biphenyl [9], diphenylamine [10], and phenanthrene [9]. The solubility of naphthalene in biphenyl and phenanthrene is ideal, and in diphenylamine close to ideal, while its solubility in methyl alcohol is considerably less than ideal. The ideal solubility of naphthalene at 20° is 0.261 and the solubility of naphthalene in methyl alcohol at the same temperature is 0.0180 [11].

Ethylpyridinium iodide also increases the solubility of naphthalene in methyl alcohol. The fusibility diagram for the system naphthalene-ethylpyridinium iodide has a region of separation from 44 to 87% of naphthalene.*

The salting-in action of diphenyl, diphenylamine, and ethylpyridinium iodide is explained by the fact that they dissolve naphthalene better than methyl alcohol.

Thus, an increase in the solubility of a non-electrolyte in a solution of certain substances in comparison with that in the pure solvent is explained by the fact that the added substances dissolve the non-electrolyte better than the solvent. A similar point of view has been put forward in the literature [12-16] as a hypothesis, but has never been developed. A reduction in the solubility will be caused by all substances (electrolytes and non-electrolytes) in which the non-electrolyte is less soluble than in the solvent in which the solubility is determined.

* Results of student É. Dontsova.

SUMMARY

1. The solubility of naphthalene in methyl alcohol and in solutions of sodium iodide and bromide, lithium chloride and perchlorate, biphenyl, diphenylamine, phenanthrene, and ethylpyridinium iodide of various concentrations has been studied.

2. Sodium iodide and bromide, lithium chloride and perchlorate, resorcinol, and urea diminish the solubility of naphthalene in methyl alcohol.

3. Biphenyl, diphenylamine, phenanthrene, and ethylpyridinium iodide increase the solubility of naphthalene in methyl alcohol.

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INVESTIGATION OF THE INTERACTION OF ZIRCONIUM CHLORIDE WITH ORGANIC ADDENDS CONTAINING VARIOUS FUNCTIONAL GROUPS

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It has been shown in a series of papers [1-5] that $ZrCl_4$ forms stable molecular compounds with esters. In the case of esters of monobasic carboxylic acids, the most characteristic composition for these compounds is 1 : 2 (more rarely 1 : 1). With esters of dibasic acids, zirconium chloride forms compounds of the 1 : 1 composition. The high polarity of the molecular compounds of $ZrCl_4$ with esters [3, 5] and the magnitude of the heat of their formation [1, 6] indicate their coordination character. In these compounds, the most characteristic coordination number for zirconium - the complex-forming agent - is six. The complex-forming power of zirconium chloride with organic compounds containing various functional groups, in spite of its practical and theoretical importance, has been investigated extremely inadequately [7].

The present paper gives the results of a study of the interaction of zirconium chloride with diethyl ether, acetone, aniline, acetonitrile, and thiophene. In addition to preparative investigations, we obtained figures on the polar properties of some of the complexes.

The method of determining the dipole moments, and also the characteristics of the zirconium chloride and benzene, have been described earlier [3]. The remaining substances used in the investigation had the following constants after careful purification:

	b.p.	d_4^{20}	n_D^{20}
$(C_2H_5)_2O$	34.5—34.7°	0.7053	1.3507
$(CH_3)_2CO$	54.6—56.6	0.7918	1.3598
$C_6H_5NH_2$	184.1—184.5	1.0218	1.5865
CH_3CN	81.8—82.1	0.7828	1.3428
C_4H_4S	84.1—84.4	1.0645	1.5285

All operations with zirconium chloride and its complexes were carried out with the observation of precautionary measures against the access of traces of moisture.

On adding zirconium chloride to diethyl ether, no visible changes took place at first. On prolonged shaking in ether in a sealed tube, the chloride gradually entered into reaction with the ether with the formation of a white microcrystalline product (small regular crystals in the form of cubes easily distinguishable under the microscope), practically insoluble in ether. The formation of a molecular compound of $ZrCl_4$ with diethyl ether took place considerably more rapidly on shaking the chloride in ether containing a small amount of benzene (1 volume of benzene to 7 volumes of ether). The white microcrystalline product of the interaction of zirconium chloride with diethyl ether isolated under these conditions, after filtration and drying had a 1 : 2 composition (Table 1) and melted in a sealed capillary with foaming at $95 \pm 3^\circ$.

When zirconium chloride is shaken with benzene containing diethyl ether at the rate of 1 mole of ether to 1 mole of the chloride, the latter dissolves completely. Separation of the solution takes place with the formation of a small lower layer containing practically all the ether and the chloride. Thus, the product formed at a molecular ratio of diethyl ether to zirconium tetrachloride of 1 : 1 is insoluble in benzene. On further addition of ether (to a molecular ratio of chloride to ether of 1 : 2) a completely homogeneous solution is obtained suitable for dielectric investigations.

TABLE 1. Results of the Analysis of the Complexes Obtained

Complex	Cl (g)		ZrO ₂ (g)	
	Found	Calc.	Found	Calc.
ZrCl ₄ · 2(C ₂ H ₅) ₂ O . .	0.375	0.372	0.327	0.323
ZrCl ₄ · 2(CH ₃) ₂ CO . .	0.402	0.406	0.351	0.353
ZrCl ₄ · 2CH ₃ CN . . .	0.445	0.451	0.394	0.391
ZrCl ₄ · 2C ₄ H ₄ S . . .	0.350	0.354	0.310	0.307

TABLE 2. Complex ZrCl₄ · 2(C₂H₅)₂O in BenzeneR_∞ = 590 cm³, R = 83 · 6 cm³, μ = 4.87D

c	c _∞	d ²⁰ ₄	P (cm ³)
0.01410	2.798	0.9024	557
0.00931	2.616	0.8944	558
0.00690	2.528	0.8905	557
0.00448	2.442	0.8862	569
0.00321	2.402	0.8840	574
0.00230	2.370	0.8825	575

Table 2 gives the results of an investigation of the dielectric permeability and density of benzene solutions of the molecular compound ZrCl₄ · 2(C₂H₅)₂O. Its dipole moment was found to be 4.87D. The increase in the dipole moment due to the formation of the complex is 3.15D.*

The dipole moment of the compound ZrCl₄ · 2(C₂H₅)₂O was also measured in benzene solutions containing the chloride and ether in a molar ratio of 1 : 4 (Table 3). The calculation of the polarization was carried out from the 1 : 2 composition, the polarization of the excess of ether being taken as 53 cm³ [9]. The curve of polarization as a function of the concentration coincides, within the limits of experimental error, with the curve constructed from the data of Table 2. Thus, the method of dielectric polarization does not detect a reaction of zirconium chloride with more than 2 molecules of diethyl ether.

In acetone, zirconium chloride dissolves rapidly with vigorous evolution of heat. A molecular compound of the composition ZrCl₄ · 2(CH₃)₂CO was obtained by shaking zirconium chloride for several hours in carbon tetrachloride containing the zirconium chloride and acetone in a ratio of 1 : 4.

The results of an analysis are given in Table 1. The product obtained forms a white microcrystalline powder (crystals distinguishable only under the microscope), melting with resinification at 125°. No appreciable decomposition of the complex was observed at room temperature. The compound obtained in carbon tetrachloride is insoluble in benzene. It begins to be appreciably soluble in benzene only with a considerable excess of acetone. With a large excess of acetone, benzene solutions acquire an appreciable electrical conductivity, which prevents the measurement of their dielectric permeability. Benzene solutions containing zirconium chloride and acetone in a molecular ratio of 1 : 15 were used to measure the dipole moment of the molecular compound. The solutions were prepared immediately before the measurements were carried out. Their dielectric permeability remained unchanged for days after preparation, within the limits of error of the measurements. This indicates the absence of an appreciable decomposition of the molecular compound.

The calculation of the dipole moment was carried out from the composition ZrCl₄ · 2(CH₃)₂CO. The polarization of the excess of acetone was allowed for in the following way. The polarization of acetone in benzene depends on the concentration. According to our results, which agree well with those in the literature [8], this dependence, within the range of concentrations present in our work, is satisfactorily represented by the equation $P_3 = 175 - 300 c_2$, where P_3 is the polarization of the acetone, and c_2 is its concentration in the solution.

* The angle between the two coordination bonds in the molecule of the complex with a 1 : 2 composition was taken as 90°, since this is done in the literature [8]. The increase in the dipole moment due to complex formation - Δμ - was calculated from the equation $\Delta\mu = \mu - \mu_1 \sqrt{2}$, where μ and μ₁ are the dipole moments of the complex and the addend.

TABLE 3. Complex $\text{ZrCl}_4 \cdot 2(\text{C}_2\text{H}_5)_2\text{O}$ in Benzene with an Excess of Diethyl Ether*

c_1	c_2	ϵ_{90}	d_{90}^{ex}	$P (\text{cm}^3)$
0.00980	0.01960	2.679	0.8916	568
0.00758	0.01516	2.581	0.8886	566
0.00485	0.00970	2.472	0.8851	562
0.00383	0.00766	2.434	0.8838	565
0.00334	0.00668	2.415	0.8831	576

* The symbols C_1 and C_2 denote the concentration of the 1 : 1 complex and the excess of addend.

In calculating the fraction of the molecular polarization of the solution due to the excess of acetone ($P_3 \cdot c_2$), the polarization of the acetone for each solution was calculated from this formula. The results of the measurements and the calculations are given in Table 4.

TABLE 4. The Complex $\text{ZrCl}_4 \cdot 2(\text{CH}_3)_2\text{CO}$ in Benzene with an Excess of Acetone*

$P_\infty = 1304 \text{ cm}^3$, $R = 70.9 \text{ cm}^3$, $\mu = 7.67 \text{ D}$.

c_1	c_2	ϵ_{90}	d_{90}^{ex}	$P (\text{cm}^3)$
0.00704	0.0916	3.998	0.8859	924
0.00473	0.0615	3.431	0.8831	1063
0.00381	0.0496	3.192	0.8820	1092
0.00261	0.0340	2.898	0.8807	1158
0.00177	0.0230	2.698	0.8800	1215

* See footnote to Table 3.

The dipole moment of this compound is 7.67 D. The increase in the dipole moment due to complex formation ($\Delta\mu$) is 3.85 D.

It is interesting to compare the increase in the dipole moment due to complex formation in the molecular compounds of zirconium chloride with various oxygen-containing addends. For formates and acetates, it amounts to 4.9–5.0 and 4.1–4.2 D, respectively [3]; for acetone it is 3.85 D, for dioxane, 5.94 D, and for diethyl ether, 3.15 D. Thus, a decrease in the polarity of the donor-acceptor bond is observed in the sequence dioxane–ester–acetone–diethyl ether. These results, to a known degree, may be considered as an indication of an increase in the donor properties of the oxygen-containing organic addends in the sequence ether–ketone–ester–dioxane.

A considerable increase in the donor properties on passing from diethyl ether to dioxane is shown also in the polarity of molecular compounds of antimony trichloride. In carbon disulfide, diethyl ether, and dioxane, the dipole moments of SbCl_3 are, respectively, 3.12, 3.90 and 5.15 D [10]. The increase in polarity in passing from the inert carbon disulfide to diethyl ether amounts to only 0.78 D, while on passing to dioxane it is more than two Debye units.

Literature data on the polarity of molecular compounds of the tetrachlorides of the metals of group IV with nitriles [10] show that the nitrile nitrogen in these compounds can act as an electron donor, thanks to which a highly polar coordination bond is formed. It is of interest to determine the donor properties of amine nitrogen with respect to the chlorides of metals of group IV. Cyclic and aromatic amines (pyridine, quinoline, aniline, diethylaniline, etc.) form molecular compounds of various compositions with titanium and tin chlorides. An investigation of the polarity of these compounds might give interesting information on the character of the link between the amines and the molecule of chloride. Meanwhile, we have found no data in the literature on the polar properties of the molecular compounds of the halides of the group IV metals with amines. It is possible that the reason for this is the serious experimental difficulty – these complexes are insoluble in the solvents usually used for the measurement of dipole moments.

Thus, according to our results, the products of the interaction of titanium and tin tetrachlorides with aniline, pyridine, quinoline, and dimethylaniline formed at a molecular ratio of chloride to amine in solutions of 1 : 1, 1 : 2, and 1 : 3 are insoluble in benzene, carbon tetrachloride, hexane, toluene, chloroform, and carbon disulfide.

At the very first, zirconium chloride reacts vigorously with dimethylaniline, pyridine, and quinoline, the surface of the chloride rapidly darkening. Then the reaction slows down markedly, which is apparently connected with the coating of the surface of the chloride with resinous products. The products of the interaction of $ZrCl_4$ with dimethylaniline, pyridine, and quinoline are insoluble in benzene. On adding zirconium chloride to aniline, again the reaction at first proceeds vigorously with a considerable evolution of heat. Then the dissolution of the chloride in the aniline proceeds more slowly, with the formation of a homogeneous solution. Aniline, pyridine, quinoline, and dimethylaniline precipitate zirconium chloride even from benzene solutions of its molecular compounds with the esters ethyl acetate and ethyl formate. The product of the interaction of zirconium chloride and acetonitrile is also insoluble in benzene. Shaking the chloride in benzene containing acetonitrile in an amount double that required for the formation of a molecular compound with a 1 : 2 composition leads to the dissolution of the chloride and the formation of a white microcrystalline product insoluble in benzene even with a considerable excess of acetonitrile. The composition of the product when it has been filtered off and dried corresponds to the formula $ZrCl_4 \cdot 2CH_3CN$ (Table 1). Shaking zirconium chloride in benzene containing aniline at the rate of 2 molecules of aniline per 1 molecule of the chloride, leads to the dissolution of the latter, and a white flocculent precipitate, insoluble in benzene separates from the solution. The addition of aniline (three and four molecules per molecule of the chloride) leads to the combination of aniline with the precipitate. On adding more aniline, the latter does not continue to combine with the chloride, as is established by analysis of the product for chlorine and zirconium. With a considerable excess of aniline with respect to that necessary for the formation of a 1 : 4 molecular compound, the product of the interaction of zirconium chloride with aniline exhibits an appreciable solubility in benzene.

We attempted to measure the dipole moment of $ZrCl_4$ in benzene solutions containing a considerable excess of aniline. The concentration of the latter in the solution was limited, on the one hand, by the low solubility of the chloride at a low content of aniline in the solution and, on the other hand, by the appearance of appreciable electrical conductivity when its content was too great. The initial solution was prepared by dissolving the chloride in a mixture of benzene and aniline. The other solutions were prepared by diluting the initial solution with benzene containing a certain amount of aniline. The results of the measurements are given in Table 5, where c_1 and c_2 are the concentrations of the chloride and aniline, expressed in molar fractions. The polarization was calculated with allowance for the free chloride. The dependence of the polarization of aniline in benzene on the concentration of the aniline (within the limits of the concentrations present in our investigations) agreed well, according to our experimental results, with the equation $P_3 = 72.7 - 7c_2$, where P_3 is the polarization of aniline in benzene. The value of P_3 for each solution was calculated from this equation.

TABLE 5. Zirconium Chloride in Mixtures of Benzene and Aniline $P_\infty = 870 \text{ cm}^3$, $R = 38.6 \text{ cm}^3$, $\mu = 6.30 \text{ D}$

c_1	c_2	ϵ_{20}	d^∞_e	$P (\text{cm}^3)$
0.01475	0.1898	3.830	0.9366	565
0.00956	0.1603	3.434	0.9219	645
0.00706	0.1461	3.229	0.9151	680
0.00479	0.1332	3.055	0.9088	743
0.00388	0.1281	2.980	0.9063	765
0.00299	0.1231	2.909	0.9038	800
0.00186	0.1167	2.807	0.9005	808

As the data of Table 5 show, the interaction of zirconium chloride with aniline takes place with the formation of a highly polar molecular compound. The presence of an excess of aniline in the solution prevents the determination of the composition of this compound.

The dipole moment of stannic chloride in a mixture of benzene and aniline was determined in a completely similar way. The results are given in Table 6.

The dipole moment obtained -4.32 D proved somewhat lower than might have been expected by analogy

TABLE 6. Stannic Chloride in Mixtures of Benzene and Aniline $P_{\infty} = 430 \text{ cm}^3$, $R = 36.2 \text{ cm}^3$, $\mu = 4.32 \text{ D}$

c_1	c_2	ϵ_{12}	d^{12}	$P (\text{cm}^3)$
0.00764	0.1723	2.985	0.9227	155
0.00509	0.1499	2.900	0.9135	231
0.00383	0.1386	2.850	0.9089	282
0.00253	0.1271	2.789	0.9040	340
0.00203	0.1226	2.760	0.9023	347
0.00146	0.1175	2.726	0.9002	351

with other molecular compounds of stannic chloride the dipole moments of which are known [10-12]. It is possible that this is explained by a trans arrangement of the Sn-N coordination bonds. The possibility is also not excluded of the presence of an equilibrium in the solution between the cis and trans configurations. The solution of this problem requires further investigations.

Molecular compounds of zirconium chloride with sulfur-containing organic addends are not described in the literature. We attempted to investigate the interaction of ZrCl_4 with thiophene. When zirconium chloride was subjected to prolonged shaking in benzene containing thiophene at the rate of 4 molecules per molecule of the chloride, the latter gradually dissolved, and a red-brown amorphous product with the composition $\text{ZrCl}_4 \cdot 2\text{C}_4\text{H}_4\text{S}$ (Table 1) precipitated from the solution. This compound does not dissolve in benzene, carbon tetrachloride, or hexane.

SUMMARY

1. The interaction of zirconium chloride with diethyl ether and acetone has been investigated. Molecular compounds of the composition $\text{ZrCl}_4 \cdot 2(\text{C}_2\text{H}_5)_2\text{O}$ and $\text{ZrCl}_4 \cdot 2(\text{CH}_3)_2\text{CO}$ have been isolated under preparative conditions and their dipole moments have been measured.
2. It has been shown that in the molecular compounds of zirconium chloride with oxygen-containing organic addends, the polarity of the coordination bond increases in the sequence diethyl ether-acetone-esters-dioxane.
3. The interaction of zirconium chloride with aniline has been investigated. The dipole moments of ZrCl_4 and SnCl_4 in mixtures of benzene and aniline have been measured.
4. Molecular compounds of zirconium chloride with acetonitrile and thiophene of the compositions $\text{ZrCl}_4 \cdot 2\text{CH}_3\text{CN}$ and $\text{ZrCl}_4 \cdot 2\text{C}_4\text{H}_4\text{S}$ have been isolated under preparative conditions.

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THE KINETICS OF THE DISSOLUTION OF INDIUM ANTIMONIDE IN NITRIC ACID

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The compositions of etching agents found empirically for indium antimonide are usually extremely complex. The presence in the etching agent of components having an oxidizing function with respect to InSb and of components dissolving the oxidation products formed are generally obligatory. Nitric acid is present in the compositions generally used as polishing and selective etching agents for InSb. In particular, a mixture of nitric, lactic, hydrofluoric acids [1], of nitric and hydrofluoric acids (1 : 1) [2], of nitric, acetic, and hydrofluoric acids and bromine, etc. are used as etching agents.

It was of both practical and theoretical interest to study the kinetics of the dissolution of the indium antimonide in nitric acid.

There is voluminous material in the literature on the question of the etching of metals; as far as concerns semiconductors, data have been published at the present time only on the dissolution of germanium in nitric acid [3, 4].

EXPERIMENTAL

A known method was used in the study of the kinetics of the dissolution of indium antimonide in nitric acid [4]. Three samples of single-crystal indium antimonide of cylindrical form with a base area of about 3-5 cm² were subjected to dissolution.* The experiments were carried out in a flask; the volume of nitric acid solution was 150 ml.

Pure-for-analysis grade nitric acid was previously freed from oxides of nitrogen by the prolonged passage of a current of air. The temperature in the thermostat was maintained constant with an accuracy of $\pm 0.2^\circ$. The sample was fixed in a glass loop. In experiments where the solution was stirred, a magnetic stirrer connected through an auto-transformer which enabled the rate of stirring to be varied was used. The rotating magnetic stirrer was at a distance of 1.5 cm from the sample. The length of the experiments was from 3 minutes to 6 hours.

The rate of dissolution was determined from the formula

$$W = \frac{1}{236.55} \cdot \frac{\Delta g}{\Delta t} \cdot \frac{g \text{-(structural unit)}}{\text{cm}^2 \cdot \text{sec}},$$

where Δg is the loss in weight of the sample (in g), Δt is the time of dissolution (in sec), S is the area of the surface of the sample, and 236.5 is the molecular weight of the structural units [InSb].

On the average, the loss in weight amounted to no more than 0.01 g. The weight of the sample was determined with an accuracy of ± 0.0002 g. The samples of indium antimonide were in the form of single-crystal n-InSb with a content of impurities of 10^{14} - 10^{16} atm/cm³. Before dissolution, the sample was polished and subjected to a preliminary etching with nitric acid. The surface of the sample was examined under a MIM-7 metallurgical microscope. Calculation of the kinetic magnitudes was carried out by the usual method [4]. Each experiment was twice repeated; the error in the determinations of the rate of dissolution of indium antimonide in nitric acid was not greater than 10%.

Single-crystal indium antimonide was dissolved in nitric acid solutions with a range of concentrations from 0.97 to 12.37 N at 20-80° both in the absence of stirring and with the solution stirred at a rate of 300-1000 rev/min. The results of the investigation are given in Fig. 1. The rates of stirring the solution are set off along the axis of abscissae, and the values of $pW = -\log W$ along the axis of ordinate.

* The single-crystal indium antimonide was obtained by the method of zone recrystallization in LFTI AN SSSR.

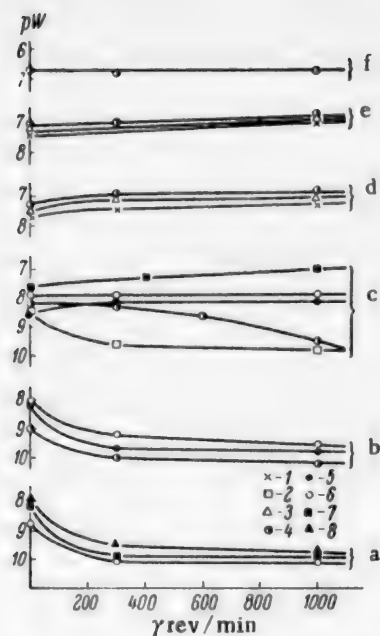


Fig. 1. Values of pW as a function of the rate of stirring γ in rev/min. Normality of the nitric acid solutions: a) 0.97, b) 2.27, c) 3.84, d) 7.05, e) 9.67, f) 12.37. At the temperatures: 1) 20°, 2) 25°, 3) 30°, 4) 40°, 5) 50°, 6) 60°, 7) 70°, 8) 80°.

Fig. 2 shows the temperature dependence of the rate of dissolution of indium antimonide in nitric acid.

On dissolution of indium antimonide in 0.7 N HNO_3 , its surface remained perfectly clean. However, in 2.27 N and 3.84 N HNO_3 solutions, a film with a crystalline character appeared, and in 7.05 N and 9.67 N HNO_3 solutions the films had an amorphous form and were readily removed on stirring the solution. The formation of films indicates an inhibition of the process of dissolution of the products of the oxidation of indium antimonide in consequence of the slow rate of diffusion.

The kinetic results on the dissolution of indium antimonide in nitric acid are given in the Table. As can be seen from Fig. 1, the rate of dissolution of single-crystal InSb in 0.97 N and 2.27 N nitric acid solutions diminishes as the rate of stirring the solution increases up to $\gamma = 300$ rev/min and then remains practically constant.

A diminution in the rate of dissolution with an increase in the velocity of stirring the solution has been noted by several authors in the dissolution of metals in nitric acid. In particular, a diminution in the rate of dissolution of germanium in 2.5-4.0 N nitric acid was explained by the authors [4] by the autocatalytic nature of the process of oxidative dissolution. In the absence of stirring, an accumulation of nitrogen dioxide takes place in the layer of solution adjacent to the surface of the germanium. Stirring the solution leads to the more uniform distribution of the nitrogen dioxide through the whole mass of the solution, which involves a decrease in the rate of dissolution of the germanium.

The similar characteristics in the dissolution of indium antimonide indicate the presence of an autocatalytic process in this case.

The dependence of the rate of dissolution of indium antimonide on stirring in a 3.84 N HNO_3 solution has a more complex character (Fig. 1): at low temperatures (25-40°) the rate of dissolution diminishes on stirring while at a higher temperature (70°) it increases. At medium temperatures (50-60°) the rate of dissolution is almost independent of the rate of stirring the solution. Thus, the character of the process of dissolution of InSb in 3.84 N HNO_3 changes markedly with the temperature.

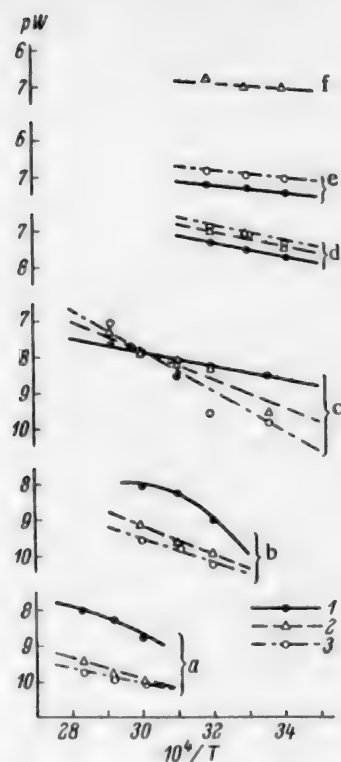


Fig. 2. Values of pW as a function of $\frac{1}{T} \cdot 10^4$. Normality of the nitric acid solutions: a) 0.97, b) 2.27, c) 3.84, d) 7.05, e) 9.67, f) 12.37. 1) without stirring, 2) stirring at a rate of 300 rev/min, 3) stirring at a rate of 1000 rev/min.

Kinetic Results on the Dissolution of Single-Crystal InSb in Nitric Acid Solutions*

Concentration of the acid (N)	Rate of stirring the solution (rev/min)	A	B	E _A kcal/mole	C ₀ structural unit/cm ² · sec.
6.97	300	3950	1.70	18.00	3.0 · 10 ²⁴
	1000	1970	-4.17	9.00	4.1 · 10 ¹⁹
2.27	300	3920	2.48	17.90	1.8 · 10 ²⁵
	1000	4100	2.90	18.70	4.8 · 10 ²⁵
3.84	Without stirring	1870	-2.21	8.50	3.7 · 10 ²¹
	300	5240	7.98	23.90	5.7 · 10 ³⁰
	1000	7100	13.64	32.40	26.2 · 10 ³⁵
7.05	Without stirring	2170	-0.32	9.90	2.9 · 10 ²³
	300	2100	-0.24	9.60	3.4 · 10 ²³
	1000	2070	-0.21	9.50	3.7 · 10 ²³
9.67	Without stirring	1240	-3.18	5.70	4.0 · 10 ²⁰
	1000	1240	-2.82	5.70	9.1 · 10 ²⁰
12.37	300	1100	-3.30	5.00	3.0 · 10 ²⁰

* A and B are the coefficients in the equation $\log W = -P_W = \frac{A}{T} + B$; E_A is the activation energy, and C_{exp} is the pre-exponential factor in the equation $W = C_{\exp} \frac{e^{-E_A/RT}}{N}$, obtained from the experimental results, E_A = 4.57 A; $C_{\exp} = e^B$; N = Avogadro's number [4].

The observed rate of dissolution must, in the first instance, be determined by the rate of oxidation of the indium antimonide by the nitric acid (W_{HNO₃}) and by the product of the reduction of nitric acid - nitrogen dioxide (W_{NO₂}):

$$W = W_{HNO_3} + W_{NO_2} = c_{HNO_3} \cdot f(\gamma) \cdot e^{-E_{HNO_3}/RT} + \frac{c_{NO_2}}{f(\gamma)} \cdot e^{-E_{NO_2}/RT} \quad (1)$$

where: c_{HNO₃} and c_{NO₂} are the concentrations of nitric acid and nitrogen dioxide, and γ is the number of revolutions of the stirrer in 1 minute.

At 25-40°, the oxidation of indium antimonide by nitric acid takes place slowly and increases considerably on passing to 60-70°.

The autocatalytic process of oxidation by the products of decomposition of the nitric acid is most intense in the absence of stirring at a low temperature. Therefore, in accordance with (1), at γ = 0 it must be expected that W_{obs} $\approx \frac{c_{NO_2}}{f(\gamma)} \cdot e^{-E_{NO_2}/RT}$, and a relatively low value of E \approx 8.5 kcal/mole is observed here. At γ = 1000 rev/min, W_{obs} $\approx c_{HNO_3} \cdot f(\gamma) \cdot e^{-E_{HNO_3}/RT}$ and a relatively high value of E - about 32 kcal/mole - is observed.

In accordance with the above, we obtain the following.

(1) At a low temperature, W_{γ=0} > W_{γ=1000}. In particular, at 25°, W_{γ=0} = 33.2 · 10⁻¹⁰ g-(structural unit)/cm²/sec, or pW = 8.5; and W_{γ=1000} = 1.4 · 10⁻¹⁰ g-(structural unit)/cm²/sec, or pW = 9.8.

(2) At a high temperature, W_{γ=0} < W_{γ=1000}. In particular, at 70°, W_{γ=0} = 2.2 · 10⁻⁸ g-(structural unit)/cm²/sec, or pW = 7.6; and W_{γ=1000} = 9.0 · 10⁻⁸ g-(structural unit)/cm²/sec, or pW = 7.0.

(3) At intermediate temperatures it is to be expected that W_{γ=0} \approx W_{γ=1000}. In fact, at 60°, W_{γ=0} = 1.35 · 10⁻¹⁰ g-(structural unit)/cm²/sec, or pW = 7.9; and W_{γ=1000} = 1.48 · 10⁻¹⁰ g-(structural unit)/cm²/sec, or pW = 7.8.

In this case, on stirring the solution, the decrease in the concentration of nitrogen dioxide at the surface of the indium antimonide will be compensated by the supply of nitric acid.

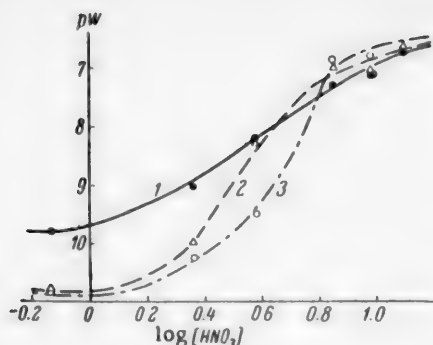


Fig. 3. pW as a function of the logarithm of the concentration of nitric acid, $\log [HNO_3]$, at 40° . 1) without stirring, 2) stirring at 300 rev/min, 3) stirring at 1000 rev/min.

The autocatalytic character of the oxidative process in 0.97-3.84 N HNO_3 solutions is characterized by a change in the relative contribution of HNO_3 and NO_2 on varying the stirring and the temperature. This explains the peculiar - at first glance irregular - change in the shape of the temperature curves a, b and c in Fig. 2 and the scatter of the values for E and C_{exp} in the Table. The uniform character of the curves in Fig. 1 and the equal slopes of the straight lines $pW = f(\frac{1}{T})$ in Fig. 2, and also the low values of C_{exp} and E in the table, observed for 7.05-12.37 N HNO_3 solutions bear witness to the diffusion character of the process which limits the rate of solution.

Fig. 3 shows the rate of dissolution of $InSb$ as a function of the concentration of the nitric acid in the absence of stirring and with stirring. With an increase in the concentration of the nitric acid, the rate of dissolution is at first slow, but in the range ~ 4 to 7 N HNO_3 , it increases rapidly, the nature of the relationship changing (intersection of the curves in this region of concentrations) and then up to 12 N HNO_3 the rate of dissolution of indium antimonide again changes little.

SUMMARY

1. The dependence of the rate of dissolution of single-crystal indium antimonide in solutions with various concentrations of nitric acid on the temperature and the rate of stirring of the solution has been investigated.
2. In dilute solutions (~ 1 -2.5 N HNO_3) the rate of dissolution of indium antimonide is determined by autocatalytic oxidation. In ~ 7 -12 N HNO_3 solutions, the rate of dissolution is limited by the diffusion of nitric acid to the surface of the indium antimonide. A concentration of about 4 N HNO_3 corresponds to the transition point.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

THE KINETICS OF THE DISSOLUTION OF INDIUM ANTIMONIDE IN HYDROCHLORIC ACID SOLUTIONS OF IRON CHLORIDE AND IODINE

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In the investigation of the kinetics of the dissolution of germanium in solutions of bromine and iodine, features were established which were explained, in considerable measure, by the covalent nature of the chemical bonds in the material studied [1]. It was of interest to carry out similar investigations of the kinetics of the dissolution of a substance with a weakly-expressed covalent component of the chemical bond. Single-crystal indium antimonide, which is characterized by a more metallic character of the chemical bond, was a suitable material for this purpose.

EXPERIMENTAL

Single-crystal n-InSb* was dissolved in hydrochloric solutions of iron chloride and iodine. Five samples of single-crystal indium antimonide, containing impurities in amounts of 10^{14} - 10^{16} atoms/cm³, were used in the investigations. The samples had a cylindrical form, the area of the base usually amounting to 3-5 cm². Dissolution was carried out in a flask, the volume of the solution being 150 ml. The flask was placed in a water thermostat, the temperature of which was maintained with an accuracy of $\pm 0.2^\circ$. The sample of indium antimonide was held in a glass loop. The rate of dissolution was found from the loss in weight of the sample taken, which was determined with an accuracy of ± 0.0002 g and, on an average, amounted to not more than 0.01 g, which gave an insignificant concentration of indium antimonide in the solutions, with practically no effect on the rate of dissolution.

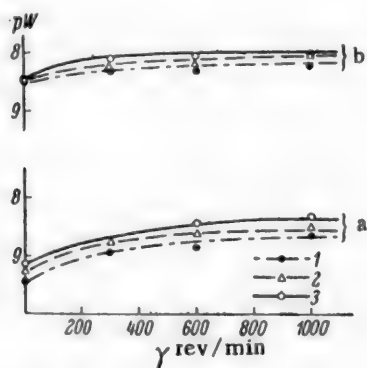


Fig. 1. pW as a function of γ .
a) 0.02 M FeCl_3 + 0.25 N HCl,
b) 0.02 M FeCl_3 + 1.00 N HCl.
1) 20° , 2) 30° , 3) 40° .

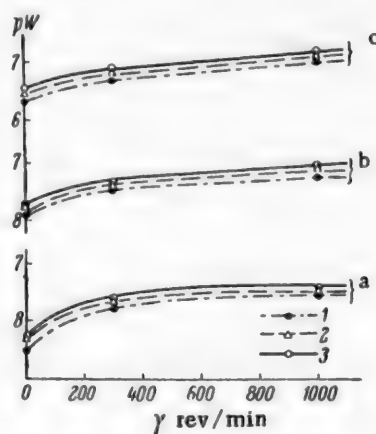


Fig. 2. pW as a function of γ .
a) 0.03 M I_2 , 2 N HCl, b) 0.15 M
 I_2 , 2 N HCl, c) 0.22 M I_2 , 2 N HCl,
1) 20° , 2) 30° , 3) 40° .

Each experiment was repeated not less than twice with different samples.

In experiments where the solution was stirred, a magnetic stirrer was used. Iron chloride hydrate, iodine, po-

* The single-crystal indium antimonide was obtained by the method of zone recrystallization in LFTI AN SSSR.

tassium iodide, and hydrochloric acid of pure-for-analysis grade were used in making the working solutions. The concentration of iron chloride in the hydrochloric acid solution was determined by the Zimmerman-Reinhardt method. The iodine was determined iodometrically, and the hydrochloric acid was titrated with alkali. Before the dissolution, the sample was subjected to a preliminary etch in the appropriate solutions, which guaranteed the establishment of a certain stationary surface with a statistically approximately constant area and reproducibility of the rate of dissolution under the given conditions. The state of the surface of the sample was checked under an MIM-7 metallurgical microscope.

The time of dissolution was recorded on a stopwatch; it was from 0.5 to 1.5 hours. The calculation of the kinetic magnitudes was carried out by the method described earlier [2].

The error in the determination of the rate of dissolution of indium antimonide was not more than 10%.

Figs. 1 and 2 give data on the relation of the magnitude $pW = -\log W$ (W is the rate of dissolution of InSb in g-(structural units)/cm²/sec) to the rate of stirring of the solution at 20, 30 and 40° in hydrochloric acid solutions of iron chloride (0.02 M FeCl₃ in 0.25 N HCl and 1.00 N HCl) and iodine (0.03-0.22 M I₂, 2 N HCl). As follows from the results given, the rate of dissolution of indium antimonide in hydrochloric acid solutions of iron chloride and iodine increased on stirring the solution and varied little at $\gamma = 400$ and 1000 rev/min.

The temperature dependence $pW = f(\frac{1}{T})$ is linear (Figs. 3 and 4).

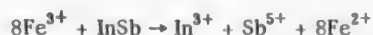
The calculated graphical coefficients A and B, and also the values of the magnitude E_A (kcal/mole) and C_{exp} (structural units/cm²/sec) calculated in the usual way, are given in Tables 1 and 2.

TABLE 1. Kinetic Figures for the Dissolution of Single-Crystal InSb in Hydrochloric Acid Solutions of Iron Chloride

Composition of the solution	Rate of stirring (rev/min)	A	B	E_A kcal/mole	C structural units/cm ² · sec.
0.02 M. FeCl ₃ + 0.25 N. HCl	Without stirring	1370	-4.77	6.30	$1.0 \cdot 10^{10}$
	600	1650	-3.18	7.50	$3.8 \cdot 10^{20}$
	1000	1750	-2.73	8.00	$1.1 \cdot 10^{21}$
0.02 M. FeCl ₃ + 1.00 N. HCl	Without stirring	250	-7.66	1.10	$1.3 \cdot 10^{10}$
	300	975	-5.00	4.40	$6.2 \cdot 10^{18}$
	600	1000	-4.91	4.60	$7.5 \cdot 10^{18}$
	1000	1000	-4.75	4.60	$1.1 \cdot 10^{19}$

The rather low values for E_A , low in comparison with $C_T^* = 6.10 \cdot 10^{26}$ structural units/cm²/sec, the values of C, and the dependence of the rate of dissolution on the stirring permit the conclusion to be drawn that the rate of dissolution of indium antimonide in hydrochloric solutions of iron chloride and iodine is limited to a considerable extent by diffusion processes.

By assuming that the process of dissolution of indium antimonide in hydrochloric acid solutions of FeCl₃ proceeds according to the equation



and using the Nernst expression for the diffusion process for the transport of Fe³⁺ ions from the solution to the surface of the solid body at room temperature [3], it is possible to calculate the rate of dissolution of indium antimonide in hydrochloric acid solutions of iron chloride approximately. The calculation gives $W_{calc} = 5.0 \cdot 10^{-9}$ g-(structural units)/cm²/sec

* C_T is the pre-exponential factor in the equation $W = C_T \cdot e^{-E_A/RT}$, calculated theoretically from $C_T \approx n_s \cdot \nu$, where n_s is the number of particles present in 1 cm², and ν is the frequency of vibrations of the atoms, equal to 10^{12} sec⁻¹ with an accuracy of about one order of magnitude [2].

TABLE 2. Kinetic Figures for the Dissolution of Single-Crystal InSb in Hydrochloric Acid (2 N HCl) Solutions of Iodine

Concentration of iodine in sol. (M)	Rate of stirring (rev/min)	A	B	E kcal mole	C structural units cm ² · sec.
0.03	Without stirring	1030	-5.00	4.70	6.0 · 10 ¹⁷
	300	950	-4.55	4.30	1.7 · 10 ¹⁹
	1000	1000	-4.18	4.60	3.9 · 10 ¹⁹
0.15	Without stirring	850	-5.01	3.90	5.9 · 10 ¹⁸
	300	700	-5.11	3.20	4.6 · 10 ¹⁸
	1000	820	-4.40	3.80	2.4 · 10 ¹⁹
0.22	Without stirring	820	-4.86	3.80	9.2 · 10 ¹⁸
	300	770	-4.68	3.50	1.3 · 10 ¹⁹
	1000	720	-4.52	3.30	3.0 · 10 ¹⁹

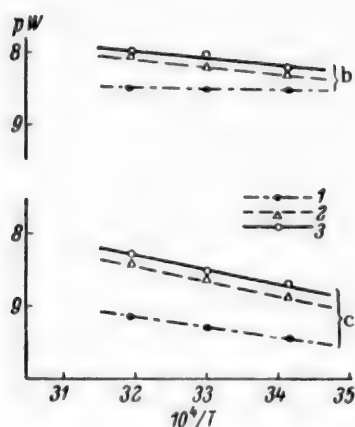


Fig. 3. pW as a function $\frac{1}{T} \cdot 10^4$

- a) 0.02 M FeCl_3 , 0.25 N HCl,
b) 0.02 M FeCl_3 , 1.00 N HCl.
1) without stirring, 2) 600 rev/min, 3) 1000 rev/min.

This value is equal, to about one order of magnitude, to the rate of dissolution of single-crystal indium antimonide in a hydrochloric acid solution of iron chloride without stirring in the experiment at 20°. Thus, we consider that the dissolution of indium antimonide in a hydrochloric acid solution of iron chloride is limited in practice by the diffusion of Fe^{3+} ions to the surface of the indium antimonide. The rate of dissolution in the 0.25 N hydrochloric acid solution of iron chloride was found to be lower than in the 1.00 N solution (Fig. 1).

This was to be expected, since a diminution in the acidity of the solution is connected with an increase in the degree of hydrolysis of the iron chloride, i.e., a diminution of the concentration of oxidizing iron ions.

As the concentration of Fe^{3+} ions is increased at a high acidity, the rate of their diffusion to the surface of the single-crystal increases. This fact is reflected in the temperature dependence of the rate of dissolution (Fig. 3). Hence, a lower value of the activation energy of the process of dissolution of indium antimonide was obtained for a 1.0 N hydrochloric acid solution of iron chloride than for a 0.25 N hydrochloric acid solution of iron chloride.

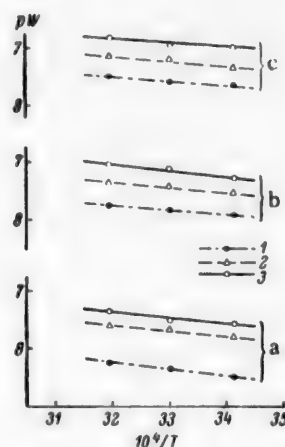


Fig. 4. pW as a function of $\frac{1}{T} \cdot 10^4$

- a) 0.03 M I_2 , 2 N HCl,
b) 0.15 M I_2 , 2 N HCl,
c) 0.22 M I_2 , 2 N HCl.
1) without stirring, 2) 300 rev/min, 3) 1000 rev/min.



Fig. 5. pW as a function of $-\log [I_2]$ a) without stirring, b) 300 rev/min, c) 1000 rev/min. 1) 20°, 2) 30°, 3) 40°.

The dependence of the rate of dissolution of InSb in solutions of iodine on the concentration of the iodine, $pW = f(-\log [I_2])$ is shown in Fig. 5. These results, however, do not offer the possibility of a more rigid determination of the order of the process with respect to the concentration of iodine. As in the case of the dissolution of germanium, the rate of dissolution of indium antimonide is determined, most probably, not by the concentration of iodine but by the concentration of hypoiodous acid.

From the value of the hydrolysis constant of iodine, $5 \cdot 10^{-13}$ [4], the volume concentration of hypoiodous acid was calculated, and from this the surface concentration n_S at the phase-separation boundary.

n_{I_2} (mole/l)	0.03	0.15	0.22
$n_S[HIO]$ (molecules per cm^2)	$5 \cdot 10^{10}$	$8 \cdot 10^{10}$	$9 \cdot 10^{10}$

The values of C_T calculated roughly prove to be four orders of magnitude higher than C_{exp} obtained from the experimental results, which also confirms the diffusion character of the dissolution of indium antimonide in hydrochloric acid solutions of iodine.

In contrast to the dissolution of indium antimonide, the rate of dissolution of germanium in iodine solutions is limited by the chemical reaction at the boundary. This difference in behavior between germanium and indium antimonide in solutions of iodine in respect of what has been said

above is connected with the fact that the covalent bonds in indium antimonide are expressed more weakly than in germanium. Indium antimonide has a more ionic-metallic character.

SUMMARY

1. The dependence of the rate of dissolution of single-crystal indium antimonide in hydrochloric acid solutions of iron chloride and iodine on the temperature and the rate of stirring of the solution has been investigated. It has been established that in the cases both of iron chloride solutions and iodine solutions the rate of dissolution of indium antimonide is limited by the diffusion process.

2. The difference in the kinetics of the dissolution of germanium and indium antimonide in iodine solutions which has been established is explained by the different degree of covalency of their chemical bonds.

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AN INVESTIGATION OF THE PROPERTIES OF AMINOACIDS AND PEPTIDES CONTAINING A TERTIARY NITROGEN ATOM

VI. A SPECTROPHOTOMETRIC INVESTIGATION OF THE COPPER COMPLEXES OF SOME N, N-DIBENZYLTRIPETIDES AND THE DETERMINATION OF THEIR COMPOSITION BY THE METHOD OF CONTINUOUS MEASUREMENT (OSTROMYSLENSKII-ZHOB)

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As we have reported earlier [1-3], N, N-dibenzyltripeptides, in distinction from peptides with a free terminal amino group, give two absorption bands - in the red (λ_{\max} 520 m μ) and in the blue (λ_{\max} 600 m μ) - in different concentrations of alkali. The present paper gives the results of further study of this question. Thus, N, N-dibenzylglycylglycylglycine and its ethyl ester and the methyl ester of N, N-dibenzylleucylglycylphenyl alanine also form two types of complexes (Table 1).

TABLE 1

Peptide	λ_{\max} (in μ) at an alkali concentration of (N)		
	0.01	0.1	1.0
N, N-dibenzylglycylglycylglycine	520	530	590
Ethyl ester of N, N-dibenzylglycylglycylglycine*	510	530	580

* In the case of the ester, the formation of the complex proceeds more slowly, the peptide itself giving an immediate color. It is possible that, under the conditions of the biuret reaction, the ester first saponifies and then forms the complex.

of a complex, we were set the task of studying the change in the optical density at the wavelengths of maximum absorption for the two types of complex on increasing the concentration of alkali from 0 to 1.0 N. The following features were noted.

(1) In a neutral medium, no copper complexes of N, N-dibenzyl peptides are found, while copper non-biuret complexes of free peptides, with the structures of the internal salt type, are observed [4, 5].

(2) Previous results on the investigation of the dependence of complex formation on the pH of the medium show that in a pH 8.4 a 0.01 M solution of the substance buffer leads to a marked reduction in the pH (to 7.3) on the formation of a complex. In a pH 10.3 buffer, the reduction of the pH is less (to pH 10.0). The reduction in the pH on complex formation is caused by the neutralization of the protons of the carboxyl and peptide bonds [6]. It can be seen in Fig. 3 that, over a certain range of pH's, the value of D_{520} does not change substantially. We use this fact to determine the ratio of copper to peptide in the complex.

(3) As Figs. 4-7 show, the intensity of absorption (D_{520}) of the complexes of N, N-dibenzyltripeptides rises sharply on increasing the concentration of alkali, passes through a maximum (D_{520} in 0.05 N NaOH) and falls. D_{590} and D_{620} , in general, rise continuously.

(4) The nature of the complex formation is shown, to a considerable degree, by the effect of the aminoacid composition of the peptide. Thus, in the case of the ethyl esters of N, N-dibenzylleucylglycylglycine and N, N-di-

The curves of the absorption spectra for N, N-dibenzylleucylglycylglycine obtained with intermediate concentrations of alkali show a weakly-expressed tendency to the formation of two maxima (Fig. 1). In the case of N, N-dibenzylleucylglycylphenylalanine, absolutely clear "two-humped" curves are obtained which gradually "straighten out" on passing to the red or blue complex (Fig. 2).

This may be considered as a supplementary indication of the existence of an equilibrium system of two complexes.

Since the optical density characterizes the concentration and, to a first approximation, the stability

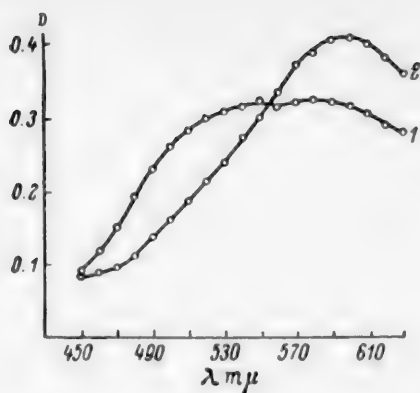


Fig. 1. Curve of the dependence of the formation copper complexes of N, N-dibenzylleucylglycylglycine on the concentration of alkali. 1) 0.05 g NaOH, 2) 0.4 g NaOH.

benzylglycylglycylglycine, the red complex forms in quite narrow ranges of the NaOH concentration (see Fig. 4-7). Conversely, for the methyl ester of N, N-dibenzylleucylglycylphenylalanine, this region is quite broad, and for the methyl ester of N, N-dibenzylleucylphenylalanylglycine, the red complex is obtained even in 1.5 N NaOH.

In the particular case of N, N-dibenzylglycylglycylglycine, we determined the composition of the red and blue complexes by the Ostromyslenskii-Zhob method, which gives the best results in the case of the determination of the composition and instability constants for the substance $\Lambda_m B_n$ [7]. The method has not been used for studying the biuret complexes of peptides.

The composition of the biuret complexes has been studied [8] for tetra-, penta-, hexa-, and heptapeptides by the methods of elementary analysis of complexes isolated in the solid state. The following results were obtained (Table 2).

M.I. Plekhan [12, 13] developed a titrimetric method for determining the ratio of copper and substance in the complex. According to these results, di-, tri-, tetra-, penta-, and hexapeptides form complexes with a ratio of Cu:peptide of 1 : 1. This is understandable, since a peptide forms a polydentate ligand.

Both the above methods of determining the composition of a complex have a serious disadvantage. In the first case, the determination involves laborious work on the isolation and purification of the complexes; in the second case, it is very difficult to obtain concordant results [13].

The prerequisites for the applicability of the method of continuous variations are the following: for the forma-

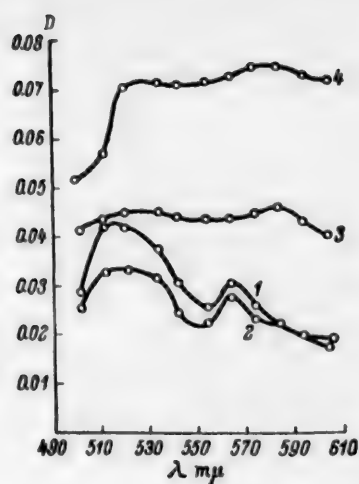


Fig. 2. Curves of the absorption spectra of copper complexes of the ethyl ester of N, N-dibenzylleucylglycylphenylalanine at various concentrations of alkali. 1) 0.2 N, 2) 0.4 N, 3) 0.8 N, 4) 1.0 N.

TABLE 2

Peptide	Peptide: Cu: NaOH ratio	Literature Data
Gly-(gly) ₂ -gly	1 : 1 : 3	[8]
Gly-(gly) ₃ -gly	1 : 1 : 3	[9]
Gly-(gly) ₄ -gly	1 : 1 : 3	[9]
Gly-(gly) ₅ -gly	1 : 2 : 4	[10]
Sarc-gly-gly-gly	2 : 1 : 4	[10]
Gly-sarc-gly-gly	1 : 1	[11]

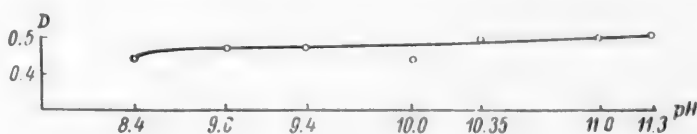


Fig. 3. Curve of the absorption spectra of the copper complexes of N, N-dibenzylglycylglycylglycine as a function of the pH of the medium at $\lambda = 520 \text{ m}\mu$.

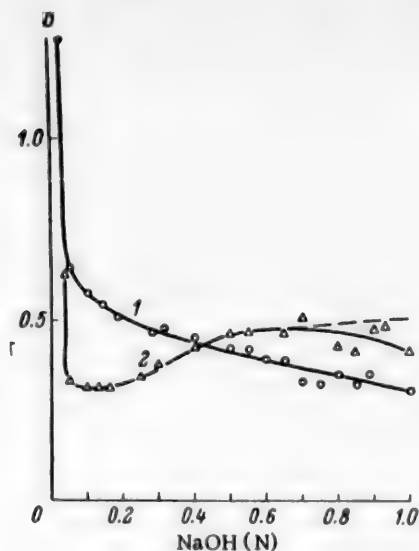


Fig. 4. Curves of the absorption spectra of copper complexes of N, N-dibenzylleucylglycylglycine as functions of the concentration of alkali. $\lambda(m\mu)$: 1) 520, 2) 590.

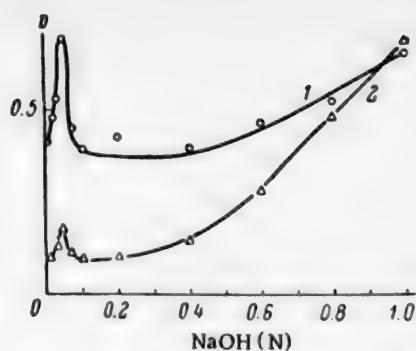


Fig. 5. Curves of the absorption spectra of copper complexes of the ethyl ester of N, N-dibenzylleucylglycylphenyl alanine as functions of the concentration of alkali. $\lambda(m\mu)$: 1) 520, 2) 590.

ly, the formation of the copper biuret complex can be represented in the following way:



i.e., there is now the $A_m B_n$ type of complex and the method of continuous variations can be used under conditions of an excess of alkali as a medium for the reaction. Under these conditions, as we have shown, the formation of the complex depends little on the pH of the medium (Fig. 3).

To determine the Cu: peptide ratio in the complex, we used one of the variants of the Ostromyslenskii-Zhob method – the method of isomolar mixtures. Isomolar solutions of the peptides and a copper salt (the sulfate in water or the chloride in alcohol) were first prepared. Mixtures with the following ratios by volume of the solutions were obtained:

First component	1	2	3	4	5	6	7	8	9	ml
Second component	9	8	7	6	5	4	3	2	1	ml

To all these mixtures was added the same amount of alkali, the following conditions being fulfilled: (1) that the concentration of alkali corresponded to a region of essentially a single complex, and (2) that the amount of OH^+ ions in the solution considerably exceeded that required for neutralizing the protons liberated on complex formation. The solutions were well stirred, allowed to stand for about 1 hour, and centrifuged. From the values of the optical density, were obtained composition-property diagrams. It was established by this method (Fig. 8) that the peptides: (1) glycylglycylglycine, (2) leucylglycylglycine, (3) chloroacetylglycylglycine, and (4) N- β -cyanoethyltriglycylglycine form complexes with a Cu: peptide ratio of 1 : 1. This agrees well with the results of other authors. We used this method also for the study of the composition of the complexes of the N, N-dibenzyl peptides. The results obtained are given in Table 3.

Obviously, the N, N-dibenzyltripeptides can give complexes of two types, which exist simultaneously in solution, their quantitative ratio depending only on the concentration of alkali. The conditions of applicability of the Ostromyslenskii-Zhob method require that only one type of complex is formed in the mixture. However, for two tripeptides (Fig. 9) we obtained absolutely sharp "peaks", these being at the 1 : 1 position. We tested a known mixture of two complexes – red and blue – formed only with N, N-dibenzylglycylglycylglycine and existing in considerable amounts

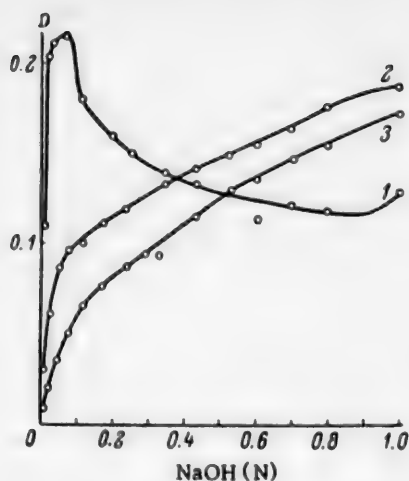


Fig. 6. Curves of the absorption spectra of the copper complexes of N, N-dibenzylglycylglycylglycine as functions of the concentration of alkali. $\lambda(\text{m}\mu)$: 1) 520, 2) 590, 3) 620.

at an NaOH concentration of 0.5 N. Here also we obtained a perfectly sharp peak with a Cu:peptide ratio of 1:1. This indicates that the ratio of the concentrations of the two complexes does not depend on the ratio of the components forming them (Cu and peptide) but depends only on the concentration of the alkali.

TABLE 3

Peptides	Concentration of alkali (N)	Cu : peptide ratio
N, N-dibenzylglycylglycylglycine	0.05	1 : 1 (Fig. 9)
	0.5	1 : 1 (Fig. 9)
	1.0	1 : 1 (Fig. 9)
Ethyl ester of N, N-dibenzylglycylglycylglycine	0.05	1 : 1 (Fig. 9)
N, N-dibenzylleucylglycylglycine	0.05	1 : 1 (Fig. 10)

It must be noted that this method is very simple and convenient: it gives clear results if the substance is pure; with impurities of the order of 1-3%, the peak in the diagram is shifted from the position of the correct ratio. For N, N-dibenzylglycylglycylglycine with an inaccurately weighed sample (0.0009 mole instead of 0.001 mole) a displacement of the peak was clearly observed. The maximum on the diagram was obtained at a Cu : peptide ratio = 4.75 : 5.25, instead of 5 : 5. The concentration of the alkali has very great importance for the case with the red complex; therefore particular care must be observed in its addition. The use of a buffer makes it possible to obtain points lying limitingly close to the two intersecting straight lines of the diagram.

For free peptides, the influence of alkali is considerably less and the accuracy higher. Therefore this method, thanks to its simplicity, and the clarity and reliability of the results, can be recommended as the method of deter-

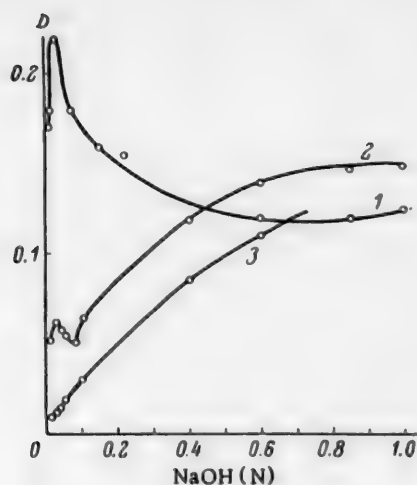


Fig. 7. Curves of the absorption spectra of the copper complexes of the ethyl ester of N, N-dibenzylglycylglycylglycine as functions of the concentration of alkali. $\lambda(\text{m}\mu)$: 1) 520, 2) 590, 3) 620.

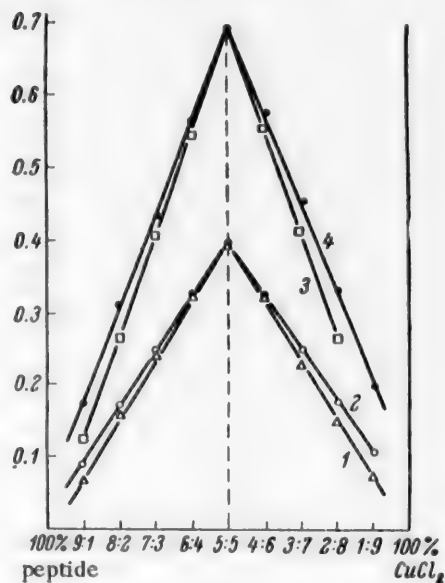
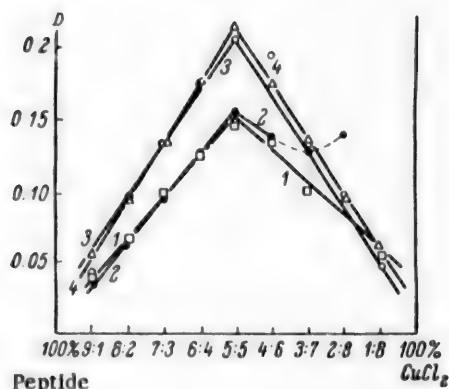


Fig. 8. Composition-property diagram for a series of isomolar solutions of copper complexes. 1) glycylglycylglycine, λ_{max} 570 $\text{m}\mu$; 2) leucylglycylglycine, λ_{max} 570 $\text{m}\mu$; 3) chloroacetyl-glycylglycylglycine, λ_{max} 550 $\text{m}\mu$; 4) N- β -cyanoethylglycylglycylglycine, λ_{max} 510 $\text{m}\mu$.

On the other hand, according to Chugaev, Kober, and Plekhan's general rule for copper complexes of the biuret type [18-20] the transition from the red to the blue complexes is connected with the substitution of oxygen for nitrogen in the coordination sphere. Therefore, leaving aside the question of the nature of the interaction of the peptide bonds with the metal and assuming the structure given by M. Rising [21], and by Murphy [22], we shall conclude only that the terminal amino group of the tripeptide participates in the complex and consider it perfectly probable that it may not participate in the formation of the complex to a greater or lesser degree, i.e., this equilibrium (for a dibenzyl tripeptide) obviously exists:



1) N, N-dibenzylglycylglycylglycine, 0.5 N NaOH; 2) ditto, 1 N NaOH; 3) ditto, 0.05 N NaOH; 4) ethyl ester of N, N-dibenzylglycylglycylglycine, 0.05 N NaOH.

It is known from the literature that the copper complexes of dialkylaminoacids have, in certain cases, a greater absorption in the red region than the complexes of the free aminoacids (for example, diethylglycine [24]). N, N-di-

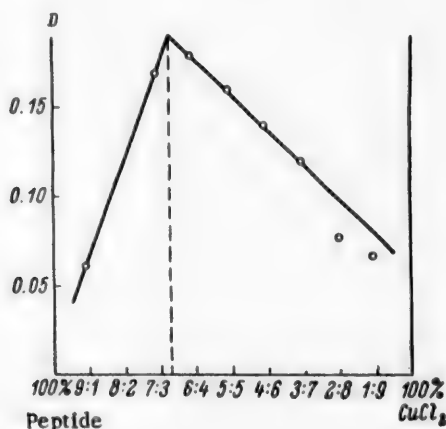


Fig. 10. Composition-property diagram for a series of isomolar solutions of the copper complexes of the ethyl ester of N, N-dibenzyleucylglycylglycine at a concentration of alkali of 0.05 N for $\lambda_{\max} = 520 \text{ m}\mu$.

ethylalanine forms violet-red crystals in the solid state, and N, N-dimethylvaline forms ruby red crystals [25, 26]. However, the dihydrate of this complex is blue [25]. N, N-dibenzylglycine and N, N-dibenzylleucine, on boiling with CuCO_3 in chloroform with the addition of water, formed red solutions of the complexes in chloroform. Consequently, in a number of cases, the terminal nitrogen atom leads to a shift of the color towards the red.

The N, N-dibenzylglycylglycylglycine complex with the structure (I) therefore has a considerably greater absorption in the red than the corresponding complex of glycylglycylglycine, but is less stable than the latter. Figs. 4-7 may be explained by the superimposition of these two factors.

In conclusion, we shall also note that our scheme does not explain a number of facts. It remains incomprehensible why N, N-dibenzyl dipeptides do not form complexes with copper and how the amino acid composition influences complex formation. These questions are best explicable if the possibility of a hindered enolization of the first peptide link is assumed, as has been noted earlier [1, 3]. In other words, the question still remains open as to what is the cause of the special nature of complex formation with the dibenzyltripeptides – the peptide link adjacent to the terminal tertiary nitrogen atom, or the terminal tertiary nitrogen atom itself.

EXPERIMENTAL

The synthesis of the substances mentioned has been described in one of the preceding communications of this series [2].

Method of preparing the solutions for spectrophotometric measurement. A solution of the substance was made in a 0.05 N solution of a copper salt (CuCl_2) in anhydrous alcohol. The solutions were added from burettes in the following order: substance, copper salt, alkali, and water. The alkali (0.1 and 2 N) was used in aqueous form in amounts sufficient to give the required concentration in 10 ml of the mixture. Water was added to a total volume of 10 ml in such amount that the ratio of alcohol to water was 1 : 1. The mixture obtained was shaken, allowed to stand for 1 hour, and centrifuged from the residue, and the clear solution obtained was used for taking the spectra on the SF-4 spectrophotometer. The amounts of reagent taken for the formation of the complexes are given in Table 4.

TABLE 4

Substance	Molarity of the solution		Amount of solution (ml)	
	substance	CuCl_2	substance	CuCl_2
Ethyl ester of N, N-dibenzylglycylglycylglycine	0.003	0.03	4.0	1.0
N, N-dibenzylglycylglycylglycine	0.005	0.05	1.0	1.5
Ethyl ester of N, N-dibenzylleucylglycylglycine	0.002	0.1	4.88	0.12
Methyl ester of N, N-dibenzylleucylglycylphenylalanine	0.005	0.03	2.0	1.0

To measure the intensity of absorption of the complexes in a buffer, we used N, N-dibenzylglycylglycylglycine hydrochloride because of its rapid solubility in water: 11 samples of the substance of 0.0132 g (0.03 mole) were each dissolved in 10 ml of buffer solution (pH from 8.0 to 11.0). The measurements of the pH values were carried out on an LP-4 potentiometer.

A 0.1 N solution of CuSO_4 was prepared. To the solution of the substance in the buffer was added 0.5 ml of the CuSO_4 solution. The mixtures obtained were treated as described above.

Complexes of dibenzylpeptides with copper. Solutions (0.05 N) of the ethyl ester of N, N-dibenzylglycylglycylglycine (weight 0.1985 g), N, N-dibenzylglycylglycylglycine (weight 0.1845 g), and the ethyl ester of N, N-dibenzylleucylglycylglycine (weight 0.2275 g) in 100 ml of anhydrous alcohol and a 0.05 N solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in 100 ml of the same alcohol were prepared. The two solutions were added from burettes, forming mixtures each having a total volume of 5 ml with ratios of the components 1 : 9, 2 : 8, 3 : 7, 4 : 6, 5 : 5, 6 : 4, 7 : 3, 8 : 2, and 9 : 1. Alkali was added to the mixtures: If a 0.05 N concentration of NaOH was required, 5 ml of 0.1 N NaOH was added; if a 0.5 N concentration of NaOH was required, 2.5 ml of 1 N NaOH and 2.5 ml of water were added; and to obtain a concentration of 1 N NaOH, 5 ml of 2 N NaOH was added. The total volume of the mixture in which the complex formed was 10 ml. The values of λ_{max} are given in Table 5.

Complexes of dibenzylglycylglycylglycine in a buffer with pH 10.4. Dibenzylglycylglycylglycine hydrochloride (0.37 g; 0.0097 mole) was dissolved in 100 ml of phosphate buffer with pH 10.7. The solution of the peptide and a 0.1 molar solution of CuSO_4 were mixed in the necessary proportions. The further procedure was as described above.

TABLE 5. Values of λ_{\max} of the Copper Complex of Dibenzyglycylglycylglycine at pH 10.4

Wave-length (m μ)	Peptide: copper ratio									
	9:1	8:2	7:3	6.5:3.5	6:4	5:5	4:6	3:7	2:8	1:9
520	0.200	0.365	0.550	0.630	0.710	0.800	0.630	0.470	0.315	0.120
530	0.205	0.375	0.560	0.640	0.720	0.810	0.640	0.480	0.312	0.125
540	0.195	0.365	0.550	0.630	0.710	0.800	0.630	0.470	0.310	0.125

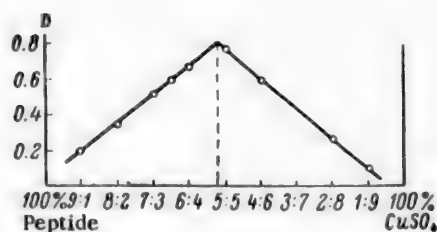


Fig. 11. Composition-property diagram for a series of isomolar solutions of the copper complexes of N, N-dibenzylglycylglycylglycine (hydrochloride) in a pH \sim 10.4 buffer for $\lambda_{\max} = 530$ m μ .

In the N, N-dibenzylglycylglycylglycine solutions, the 2:8 and 1:9 mixtures remained turbid and after centrifuging the absorption increased on account of this (Fig. 11, Table 5).

Complexes of the other peptides. Solutions of the peptides and CuSO_4 (0.01 molar) in water were prepared, and these solutions were mixed in the necessary ratios in such amounts that the total volume was 10 ml. Sodium hydroxide (1 ml, 2 N) was added to the mixtures. The results are given in Fig. 8.

SUMMARY

1. The influence of the concentration of alkali on the intensity of the maximum light absorption of a suitable complex of an N, N-dibenzyltripeptide has been investigated.
2. The Ostromyslenskii-Zhob method has been used to determine the quantitative ratio of copper and peptide in the biuret complex.
3. Dibenzyglycylglycylglycine and its ethyl ester form red and blue complexes containing 1 atom of Cu per 1 mole of peptide (or ester). The red complex of the ethyl ester of dibenzylleucylglycylglycine has a peptide: Cu ratio of 2:1.
4. The complexes of certain peptides - (a) with free amino groups, (b) with an acyl substituent, and (c) with an alkyl substituent - are formed with a peptide: Cu ratio of 1:1.
5. Consideration of the question of the structure of the complexes formed has been continued. The hypothesis has been put forward that the terminal tertiary amino group causes a marked shift of the absorption towards the red and simultaneously diminishes the strength of the bond of the terminal group with nitrogen, which is linked with its withdrawal from the coordination sphere.

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INVESTIGATION OF THE PROPERTIES OF AMINOACIDS AND PEPTIDES CONTAINING A TERTIARY NITROGEN ATOM

VII. COMPARISON OF THE ABSORPTION SPECTRA OF COPPER COMPLEXES OF N, N-DIBENZYL TETRAPEPTIDES CONTAINING PROLINE AND SARCOSE

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As has been shown earlier [1], the presence of two types of complexes of N, N-dibenzylpeptides is manifested in different ways according to the aminoacid composition. Obviously, in all cases, the spatial configuration and interaction between the atoms of the molecule is important.

The complexity of the question of the internal structure of a complex appears particularly marked when there are two tertiary nitrogen atoms in the molecule, particularly when proline is present in the compound, since, because of the cyclic nature of this aminoacid, the conformation of the chain alters. This may be observed by comparing the results for N, N-dibenzyltetrapeptides containing proline or sarcosine as the fourth aminoacid. When proline is included in the polypeptide chain, the process of complex formation takes place extremely slowly, and with an excess of alkali a gradual shift of the absorption maximum towards the shorter wavelengths, with an increase in the intensity of the absorption, is observed.

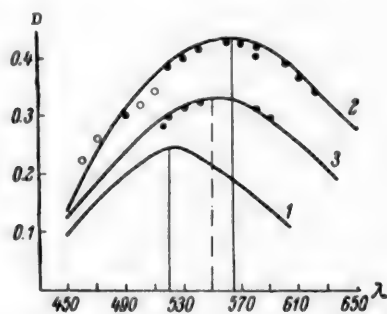


Fig. 1. Absorption spectra: 1) 0.01 mole of the methyl ester of N, N-dibenzylleucylglycylproline (0.05 g NaOH), 2) 0.01 mole of the methyl ester of N, N-dibenzylleucylglycylproline (0.5 g NaOH), 3) 0.01 mole of the methyl ester of leucylglycylproline (0.5 g NaOH). $\Delta\lambda = 50 \text{ m}\mu$.

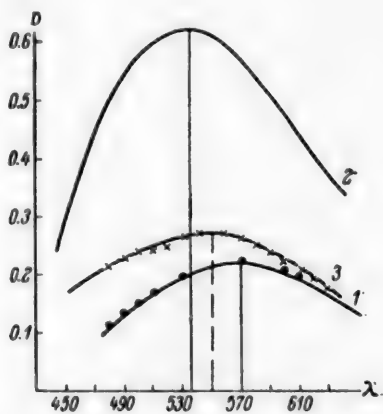
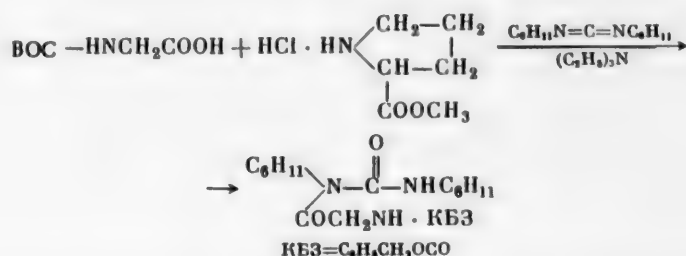


Fig. 2. Absorption spectra: 1) 0.01 mole of the ethyl ester of N, N-dibenzylleucylglycylsarcosine (0.5 g NaOH), 2) 0.01 mole of the ethyl ester of N, N-dibenzylleucylglycylsarcosine (0.05 g NaOH), 3) 0.01 mole of the ethyl ester of leucylglycylsarcosine (0.5 g NaOH).

On replacing proline by sarcosine (Figs. 1 and 2) the shift of λ_{max} is $30 \text{ m}\mu$, but the complex is formed immediately, in consequence of which it may be assumed that proline changes the structure of the polypeptide chain and, consequently, also changes the nature of complex formation. When sarcosine is present in the polypeptide chain, an absorption spectrum with λ_{max} lying between the values

of λ_{\max} of the absorption spectra of tri- and tetrapeptides is obtained. In this connection, it may be supposed that the change in the nature of the absorption spectrum with time in the case of gramicidin C is connected with the presence of proline, thanks to which the copper complex undergoes structural changes, breaking the hydrogen bond formed as a result of a transannular effect - an NH-CO link - and the formation of a microcycle within the macrocyclic structure of the decapeptide. The question of the magnitude of the intensity of absorption we shall not consider yet, since it remains unexplained.

In the present work we have synthesized peptides containing tertiary nitrogen atoms. Proline and sarcosine were present as terminal aminoacids. The ethyl ester of N, N-dibenzylleucyldiglycylsarcosine was obtained and its copper complexes were studied in comparison with the complexes of the methyl ester of N, N-dibenzylleucyldiglycylproline. The most convenient method for the synthesis of these peptides proved to be the combination of N, N-dibenzylleucylglycylglycine with the hydrochloride of the ethyl ester of sarcosine or the hydrochloride of the methyl ester of proline by Boissonas' method [3]. An attempt to obtain esters of benzyloxycarbonylglycylproline or benzyloxycarbonylglycylsarcosine in aqueous dioxane using dicyclohexylcarbodiimide [4] led to the formation of an acyl-substituted dicyclohexylurea.



In this case, N-(N-benzyloxycarbonylglycyl)-N, N'-dicyclohexylurea was isolated as the main reaction product. This compound has m.p. 140-142°, and after hydrolysis with 20% HCl gave a single spot, corresponding to glycine, on the chromatogram in the butanol-water-acetic acid (4 : 5 : 1) system. Sarcosine and proline were not shown up by ninhydrin.

The formation of such acyl ureas as by-products in the carbodiimide synthesis has been broadly treated by Khorana [5].

EXPERIMENTAL

The ethyl ester of N, N-dibenzylleucylglycylglycine was synthesized by the method described in [2], by the condensation of the mixed anhydride of N, N-dibenzylleucine with the hydrochloride of the ethyl ester of glycylglycine in the presence of triethylamine. The yield was 76%, m.p. 113-114°.

N, N-dibenzylleucylglycylglycine was obtained by saponifying 1.6 g of the ethyl ester of N, N-dibenzylleucyldiglycine in 16 ml of methyl alcohol with 20.9 ml of 2 N NaOH for 13 hours at room temperature. The substance was isolated by acidification with acetic acid. The yield was 0.93 g (62%), m.p. 163-165°. According to the data of [2]: m.p. 164-165°.

Ethyl ester of N, N-dibenzylleucyldiglycylsarcosine. N, N-dibenzylleucyldiglycine (0.3 g) was dissolved in 5 ml of anhydrous chloroform and 0.1 ml (0.072 g) of anhydrous triethylamine. After cooling to -50°, 0.07 ml (0.08 g) of chlorocarbonic ester was added and the mixture was allowed to stand for 15 minutes. Then 0.15 g of the hydrochloride of the ethyl ester of sarcosine in 2 ml of anhydrous chloroform and 0.14 ml (0.1 g) of anhydrous triethylamine were added and the mixture was allowed to stand overnight. The solution was filtered, washed with water, 1 N NaHCO₃, and water, and dried with anhydrous sodium sulphate. The oil remaining after evaporation of the solvent *in vacuo* was dissolved in a small amount of methanol, the solution was filtered, and water was added until the solution became slightly turbid. After evaporation of the alcohol, the dibenzyltetrapeptide ester crystallized. No contamination with sarcosine ethyl ester was found in the electropherogram of the substance (potential gradient 6.6 V/cm). The yield was 0.15 g (40%), m.p. 97-99°.

Found %: C 66.43, 66.65; H 7.76, 7.78; N 10.36, 10.23. C₂₉H₄₀O₅N₄. Calculated %: C 66.41; H 7.63; N 10.68.

Ethyl ester of leucyldiglycylsarcosine. The ethyl ester of N, N-dibenzylleucyldiglycylsarcosine (0.2 g) was hy-

drogenated for 3 hours at 50° in 6 ml of 80% acetic acid with 0.1 g of Pd black. The filtered solution was evaporated in vacuo. The residual oil, under ether, changed into a white hygroscopic substance. The yield was 65 mg (50%).

Found %: N 15.13, 15.27. $C_{15}H_{20}O_5N_4 \cdot H_2O$. Calculated %: N 15.47.

On chromatography in the butanol-water-acetic acid (4 : 5 : 1) system with the ethyl ester of N, N-dibenzylleucyldiglycylsarcosine ($R_f = 0.92$) and leucyldiglycine ($R_f = 0.45$) as markers, a single spot with $R_f = 0.65$ was observed. The substance was hydrolyzed with 20% HCl and the hydrolyzate was chromatographed in the systems butanol-water-acetic acid (4 : 5 : 1), and 77% ethanol. Glycine, leucine, and sarcosine were found.

The methyl ester of N, N-dibenzylleucyldiglycylproline was obtained in a similar manner to the preceding substance from 0.3 g of N, N-dibenzylleucyldiglycine, 0.1 ml (0.072 g) of anhydrous triethylamine, and 0.07 ml (0.08 g) of chlorocarbonic ester by combination with 0.18 g of the hydrochloride of proline methyl ester and 0.15 ml (0.11 g) of anhydrous triethylamine in anhydrous chloroform. Purification was similar to that described above. An oil was obtained which changed into an amorphous powder after treatment with ether. The yield was 0.18 g (47%).

Found%: C 66.60, 66.59; H 7.76, 7.52; N 10.33, 10.13. $C_{30}H_{40}O_5N_4$. Calculated %: C 67.16; N 7.46; N 10.45. $R_f = 0.92$ (butanol-water-acetic acid, 4 : 5 : 1).

In the chromatogram of a hydrolyzate of the N, N-dibenzyltetrapeptide ester obtained with the same system, glycine, proline, and N, N-dibenzylleucine were found.

Preparation of the copper complexes. A sample of the substance was dissolved in a few millilitres of 96% alcohol, and a predetermined amount of crystalline caustic potash, 0.2-0.5 ml of a 0.01 M solution of $CuCl_2 \cdot 2H_2O$ in 96% alcohol were added, and the volume of the solution was made up to 10 ml. The amount of substance taken was such that, after dilution, a 0.01 M solution was obtained. The solution of copper salt was best added not immediately but after the substance had stood for some hours in the alcoholic alkali solution. Under these conditions, the intensity of the complex was considerably higher, since the hydrolysis of the ester group was complete.

After the addition of the copper chloride, the solution was allowed to stand for 1 hour and was then centrifuged. All the spectrophotometric determinations were carried out on an SF-4 spectrophotometer.

1. The copper complex of the ethyl ester of N, N-dibenzylglycylsarcosine. Complexes were obtained with λ_{max} 537 and 570 $m\mu$.
2. The copper complex of the ethyl ester of leucyldiglycylsarcosine, λ_{max} 550 $m\mu$.
3. The copper complex of the methyl ester of N, N-dibenzylleucyldiglycylproline. Complexes were obtained with λ_{max} at 520 and 565 $m\mu$.

SUMMARY

1. Tetrapeptides not described in the literature have been obtained - the ethyl ester of N, N-dibenzylleucyldiglycylsarcosine and the methyl ester of N, N-dibenzylleucyldiglycylproline.
2. The absorption spectra of these peptides have been studied and the influence of the proline residue on the nature of the complex formation of N, N-dibenzyl-substituted tetrapeptides in comparison with sarcosine has been established.

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SYNTHESIS AND CATALYTIC DECOMPOSITION OF 3, 4-DIHYDROPHTHALAZINES

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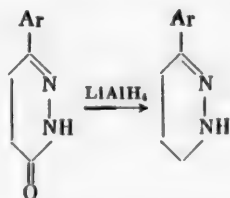
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 8,

pp. 2478-2482, August, 1961

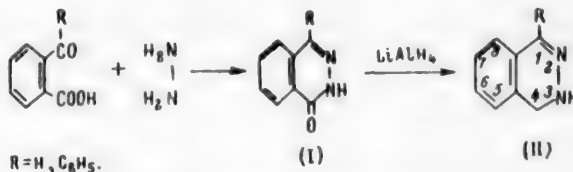
Original article submitted August 2, 1960

3,4-Dihydrophthalazine has not been described in the literature and no methods for its synthesis exist.

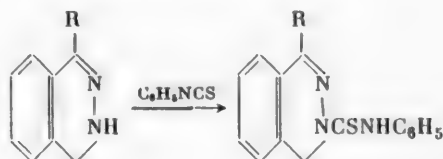
In one of our previous papers, we described a new method for the synthesis of aryltetrahydropyridazines – the reduction of 6-aryl-4,5-dihydropyridazones with lithium aluminium hydride [1]; it was shown that the carbonyl group in the latter compounds is readily reduced to a methyl group (i.e., the reaction proceeds as in the case of the reduction of acid amides to amines [2]), and that the double carbon-nitrogen bond is not attacked during the reduction.



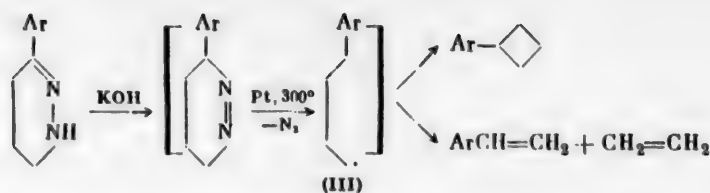
In the present investigation, this reaction has been used to obtain analogs of the tetrahydropyridazines – the 3,4-dihydrophthalazines (II). The phthalazones (I) obtained by the reaction of *o*-acylbenzoic acids with hydrazine were subjected to reduction.



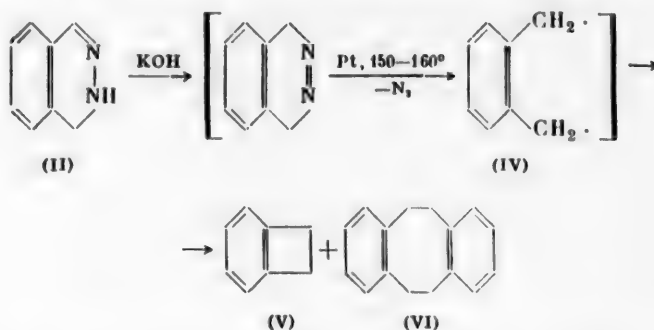
The presence of a single NH group in the 3,4-dihydrophthalazines formed was shown by the production of their products of addition with a single molecule of phenyl isothiocyanate.



The 3,4-dihydrophthalazines (II) obtained were subjected to catalytic decomposition – heating in the presence of caustic soda and platinum. We have shown earlier, that 3-aryl-1,4,5,6-tetrahydropyridazines decompose under these conditions at 280-300° with the evolution of nitrogen and the formation of arylcyclobutanes and arylethylenes [3].

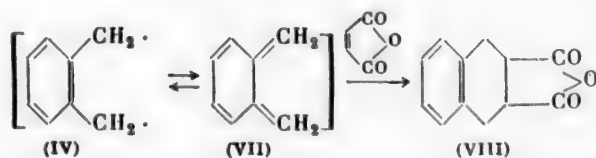


The decomposition of 3,4-dihydrophthalazines proceeds with the evolution of nitrogen at 150-160°, i. e., considerably more readily than in the case of the tetrahydropyridazines. Benzocyclobutene (V, 60%) and 1:2, 5:6-di-benzocycloocta-1,5-diene (VI, 40%) were isolated from the decomposition products of dihydrophthalazine (II, R = H). It follows that the decomposition of 3,4-dihydrophthalazine takes place according to the following scheme:

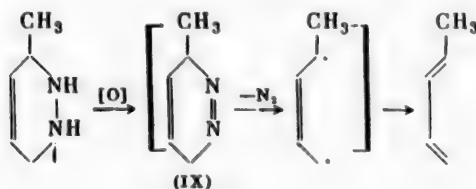


Thus, the biradicals (III) and (IV) which differ in their structure, are stabilized differently: (III), in addition to ring closure to a four-membered ring, decomposes to ethylene and styrene, and (IV) dimerizes.

The same behavior of the biradical (IV), formed in the pyrolysis of a cyclic sulfone, has also been observed by American authors [4]. The biradical (IV), formed in the decomposition of dihydrophthalazine, is also capable of reacting as a diene (VII): on carrying out the reaction in the presence of maleic anhydride, the adduct (VIII) was obtained, and no benzocyclobutene was observed.

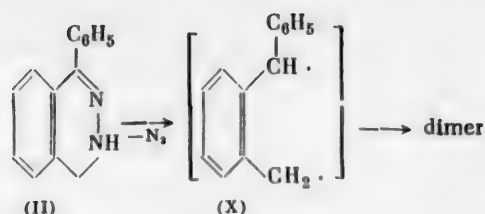


The capability of biradicals similar to (IV) to change into dienes had previously been established by us in an attempt to synthesize cyclobutenes by the decomposition of alkyl dihydropyridazines (analogs of the dihydrophthalazines) [5], obtained by the oxidation of 1,2,3,6-tetrahydropyridazines. These compounds (IX) proved to be extremely unstable and spontaneously decomposed with the evolution of nitrogen and the formation of the corresponding diene.

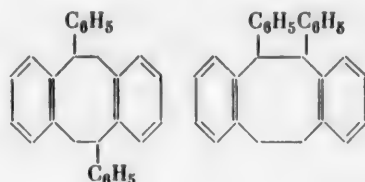


The American authors, carrying out the pyrolysis of a cyclic sulfone in the presence of N-phenylmaleimide, also noted the capability of the biradical (IV) of taking part in the diene synthesis [4].

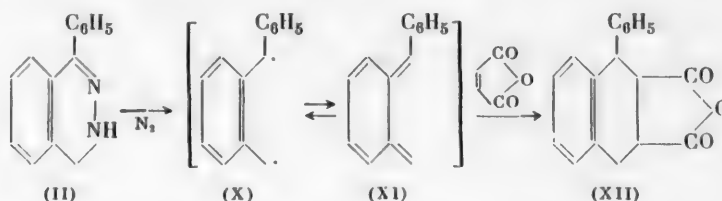
Phenylbenzocyclobutene could not be obtained by the decomposition of 1-phenyl-3,4-dihydrophthalazine (II, R = C₆H₅) under the conditions mentioned above: the biradical (X) formed as an intermediate was converted completely into the dimer.



The dimer apparently consists of a mixture of isomeric diphenyl-1:2, 5:6-dibenzocycloocta-1,5-dienes formed from the biradical (X) and differing in the position of the phenyl groups.



The decomposition of phenyldihydrophthalazine (platinum and caustic potash, 150-160°) in the presence of maleic anhydride also led to the formation of an adduct (XII; yield, 95%).



EXPERIMENTAL

***o*-Acylbenzoic acids.** Phthalaldehydic acid was obtained by the oxidation of naphthalene to phthalazonic acid with subsequent decarboxylation by the action of sodium bisulfite. Yield, 4%; m.p. 94-95° (from benzene). Literature data [6]: m.p. 96-96.5°.

***o*-Benzoylbenzoic acid** was synthesized from benzene and phthalic anhydride by the Friedel-Crafts reaction. Yield, 97%; m.p. 126-127°. Literature data [7]: m.p. 127°.

Phthalazones (I). A mixture of equimolar amounts of *o*-acylbenzoic acid and hydrazine hydrate in methyl alcohol was heated for 3 hours and the crystals depositing after the reaction mass had cooled were separated off with suction. Phthalazone (I, R = H, yield 85%): m.p. 182-183° (from alcohol). 1-Phenylphthalazone (I, R = C₆H₅, yield 87%): m.p. 235-236° (from alcohol). Literature data, respectively [8]: m.p.'s 183 and 236°.

Synthesis of 3,4-dihydrophthalazines. The reduction of the phthalazones with lithium aluminum hydride was carried out in a similar manner to the reduction of dihydropyridazones [1]. **3,4-Dihydrophthalazine** (II, R = H, yield 62%): m.p. 47-48° (from petroleum ether). Thiourea derivative with phenyl isothiocyanate: m.p. 212-213° (from a mixture of acetone and ligroin).

Found %: C 67.12, 67.24; H 4.77, 4.68. C₁₅H₁₃N₃S. Calculated %: C 67.38; H 4.90.

1-Phenyl-3,4-dihydrophthalazine (II, R = C₆H₅, yield 73%): m.p. 67-68° (from ligroin).

Found %: C 81.00, 81.05; H 6.14, 6.06. C₁₄H₁₂N₂. Calculated %: C 80.74; H 5.81.

Thiourea derivative with phenyl isothiocyanate: m.p. 174.5-175.0° (from a mixture of acetone and ligroin).

Found %: C 73.42, 73.67; H 4.90, 5.08; N 12.45, 12.48. C₂₁H₁₇N₃S. Calculated %: C 73.44; H 4.99; N 12.24.

Catalytic decomposition of 3,4-dihydrophthalazines. In a Wurtz flask were placed 6.6 g (0.05 mole) of 3,4-dihydrophthalazine, 0.2 g of caustic potash, and 0.05 g of the platinum catalyst, and the mixture was heated at 150-160° until the evolution of gas ceased. Simultaneously, benzocyclobutene distilled off. The residue was dissolved in benzene, washed with hydrochloric acid (1 : 1), dried, and boiled over sodium, and, after the benzene had been distilled off, the residue was recrystallized from ligroin.

Benzocyclobutene (V, yield 48%): b.p. 148-149° (751 mm), n_D^{20} 1.5425, d_4^{20} 0.9577. Literature data [9]: b.p. 150° (748 mm), n_D^{20} 1.5409, d_4^{20} 0.957.

1:2, 5:6-Dibenzocycloocta-1,5-diene (VI, yield 32%): m.p. 105.5-106.5°. Literature data [10]: m.p. 106.8-108.1°.

1-Phenyl-3,4-dihydrophthalazine was decomposed in the same way as 3,4-dihydrophthalazine, with the sole difference that in this case no liquid reaction products distilled off. The treatment of the catalyzate was carried out similarly.

Diphenyl-1:2, 5:6-dibenzocycloocta-1,5-diene Possibly a mixture of isomers, yield 86%): m.p. 145-146° (from ligroin).

Found %: C 93.11, 93.05; H 6.70, 6.59. $C_{28}H_{24}$. Calculated %: C 93.29; H 6.71.

Catalytic decomposition of 3,4-dihydrophthalazines in the presence of maleic anhydride. A mixture of equimolar amounts of dihydrophthalazine and maleic anhydride was heated in the presence of caustic potash and platinum at 150-160° until the evolution of gas (nitrogen) ceased; the residue was recrystallized from benzene. In this way, the decomposition of 3,4-dihydrophthalazine led to the anhydride of 1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic acid (VIII, yield 91%): m.p. 181-182°. Literature data [11]: m.p. 183°.

The decomposition of 1-phenyl-3,4-dihydrophthalazine under the given conditions yielded the anhydride of 1-phenyl-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic acid (XII, yield 95%): m.p. 170-171°. Literature data [11]: m.p. 171-172°.

SUMMARY

1. A method for the synthesis of the previously unreported 3,4-dihydrophthalazines has been developed.
2. Under conditions of catalytic decomposition (caustic potash, platinum), 3,4-dihydrophthalazine readily decomposes with the liberation of nitrogen.
3. The biradical formed in the decomposition of 3,4-dihydrophthalazine is stabilized by conversion into benzocyclobutene and 1:2, 5:6-dibenzocycloocta-1,5-diene. The biradical from 1-phenyl-3,4-dihydrophthalazine gives only the dimerization product - diphenyl-1:2, 5:6-dibenzocycloocta-1,5-diene (possibly as a mixture of isomers).
4. In the decomposition of 3,4-dihydrophthalazine under the same conditions but in the presence of maleic anhydride, the biradical reacts as a diene, forming only the adduct of the diene synthesis.

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CYCLOPROPANES AND CYCLOBUTANES

XIX. CATALYTIC DECOMPOSITION OF 3-ARYLTETRAHYDROPYRIDAZINES CONTAINING A NITRO, AMINO, OR HYDROXY GROUP IN THE PARA POSITION

Yu. S. Shabarov, N. I. Vasil'ev and R. Ya. Levina

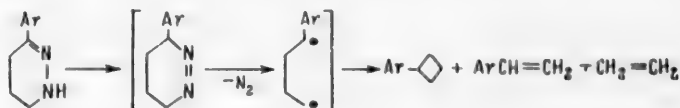
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pp. 2482-2487, August, 1961

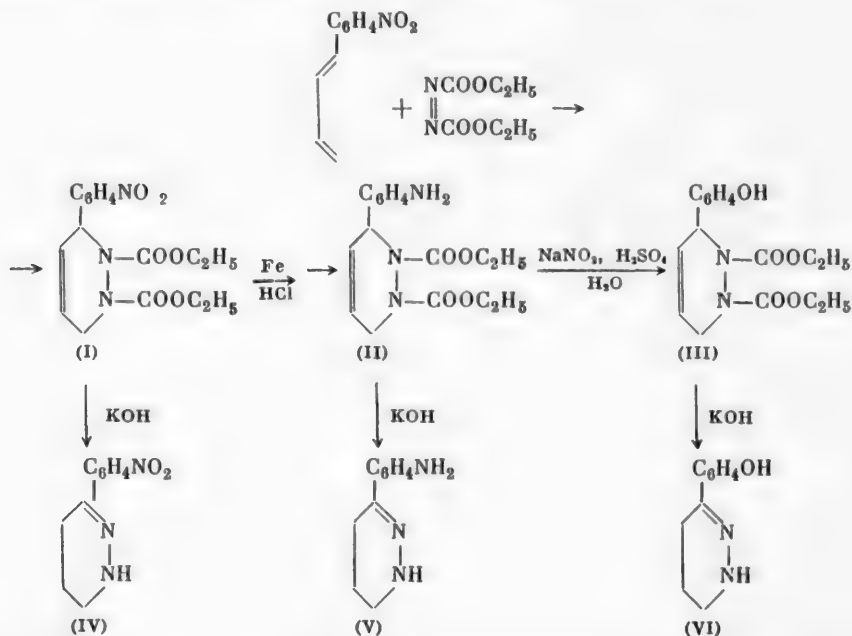
Original article submitted August 2, 1960

We have shown previously [1] that 3-aryl-1,4,5,6-tetrahydropyridazines decompose on heating to 250-300° in the presence of caustic potash and platinum with the evolution of nitrogen and ethylene and the formation of arylcyclobutanes and arylethylenes.



All the 3-aryltetrahydropyridazines investigated decomposed under the conditions given above according to the scheme shown; only the ratio of the amounts of arylcyclobutane and arylethylene (styrene) formed varied according to the structure of the tetrahydropyridazines.

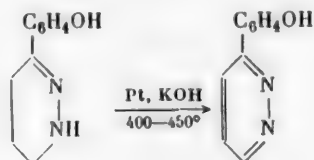
In the present investigation, the catalytic decomposition of 3-phenyltetrahydropyridazines containing nitro, amino and hydroxyl groups in the para position of the benzene ring have been studied. To synthesize these aryltetrahydropyridazines we used the method used by us previously for the production of *p*-chlorophenyltetrahydropyridazine [3] - the synthesis of 1,2-diethoxycarbonyl-3-*p*-nitrophenyltetrahydropyridazine, its reduction to the *p*-aminophenyltetrahydropyridazine, and the introduction of the hydroxyl group by the diazo reaction.



p-Aminophenyltetrahydropyridazine readily oxidized in air and was characterized by its addition product with phenyl isothiocyanate, but *p*-nitro- and *p*-hydroxyphenyltetrahydropyridazines were kept in the air without change.

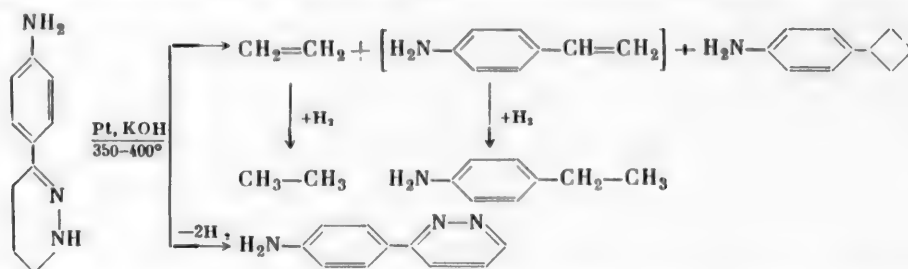
Experiments on the catalytic decomposition of the tetrahydropyridazines synthesized showed that they are very stable and, judging by gas evolution, begin to decompose only at 350–450°, i.e. 100° higher than the aryltetrahydropyridazines studied earlier. (Scheme on previous page.)

In the decomposition of 3-*p*-hydroxyphenyltetrahydropyridazine, only dehydrogenation took place. This was confirmed both by the analysis of the gas evolved in the reaction and by an investigation of the reaction products. The gas consisted solely of hydrogen, and the catalyzate consisted of 3-*p*-hydroxyphenylpyridazine (described in the literature).

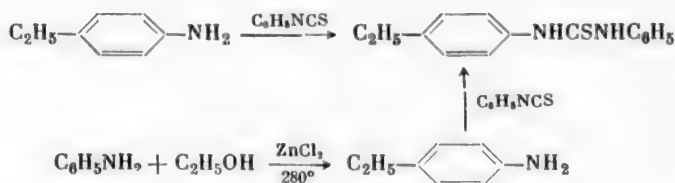


Analysis of the gases liberated in the decomposition of 3-*p*-aminophenyltetrahydropyridazine showed that they contained hydrogen, saturated hydrocarbons, ethylene, and nitrogen. By separately determining methane and its homologues, it was found that the saturated hydrocarbons contained in the gas did not include methane.

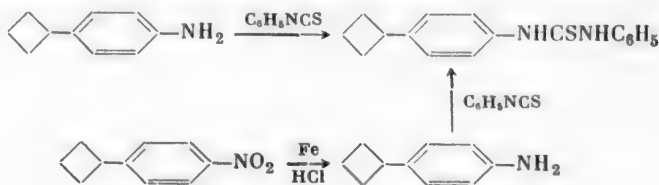
These results permitted the assumption that, in the decomposition of *p*-aminophenyltetrahydropyridazine, in addition to the normal scheme (the formation of an arylcyclobutane and the corresponding styrene, accompanied by the evolution of nitrogen and ethylene), dehydrogenation of the tetrahydropyridazine and hydrogenation (platinum being present in the reaction mixture) of the ethylene and *p*-aminostyrene formed by the hydrogen liberated takes place.



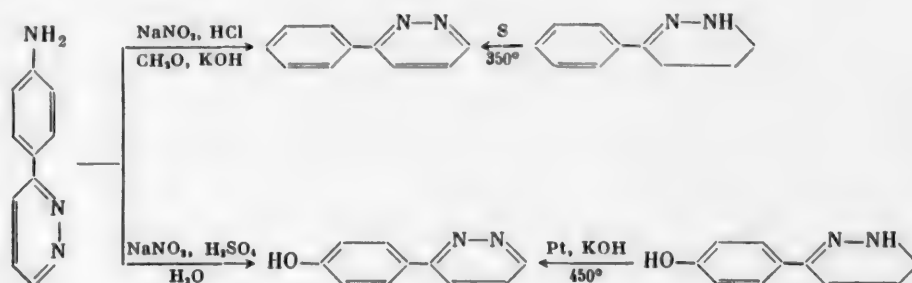
The results obtained on studying the liquid and solid reaction products confirmed this assumption. The low-boiling fraction isolated from the reaction mixture consisted, judging from its constants, of *p*-ethylaniline. The latter was identified in the form of its addition product with phenyl isothiocyanate, which was also obtained by an independent method.



p-Aminophenylcyclobutane was isolated from the high-boiling fraction and characterized by its addition product with phenyl isothiocyanate. The latter proved identical with the substance obtained from *p*-aminophenylcyclobutane prepared by the reduction of the corresponding nitro compound [3].



The distillation residue proved to be *p*-aminophenylpyridazine – the product of the dehydrogenation of the initial tetrahydropyridazine. The structure of this compound was shown by its conversion to 3-phenyl- and 3-*p*-hydroxyphenylpyridazine.



3-*p*-Nitrophenyl-1,4,5,6-tetrahydropyridazine is still more stable to the action of caustic potash and platinum at high temperatures and begins to decompose only above 475° . The gas liberated in the reaction consists solely of hydrogen. A large part of the reaction mixture carbonizes. The reaction products were found to contain aniline and a substance of the composition $\text{C}_{18}\text{H}_{18}\text{ON}_4$, the structure of which could not be established.

EXPERIMENTAL *

p-Nitrophenylbutadiene was obtained by the condensation of *p*-nitrobenzenediazonium chloride with divinyl in the presence of cupric chloride, with subsequent dehydrochlorination of the 4-chloro-1-*p*-nitrophenylbut-2-ene by the method of [2]. The yield was 70%, m.p. $77-78^\circ$ (from ligroin). Literature data [2]: m.p. $78-78.8^\circ$.

1,2-Diethoxycarbonyl-3-*p*-nitrophenyl-1,2,3,6-tetrahydropyridazine (I) was obtained by the diene synthesis from *p*-nitrophenylbutadiene and azodicarboxylic ester by the method described by us in [3]. The yield was 90-95%, m.p. $83-84^\circ$ (from ligroin). Literature data [3]: m.p. $84.0-84.5^\circ$.

1,2-Diethoxycarbonyl-3-*p*-aminophenyl-1,2,3,6-tetrahydropyridazine (II) was obtained by the reduction of the nitro compound by the method described earlier [3]. The yield was 90%, m.p. $85-86^\circ$ (from ligroin). Literature data [3]: m.p. $85-86^\circ$.

1,2-Diethoxycarbonyl-3-*p*-hydroxyphenyl-1,2,3,6-tetrahydropyridazine (III). Thirty grams (0.09 mole) of the amino compound (II) was dissolved in a mixture of 100 ml of concentrated sulfuric acid and 150 ml of water; the solution was cooled and 7 g (1.10 mole) of sodium nitrite in 20 ml of water was added at $-5--2^\circ$. The solution of the diazonium salt was heated at $50-60^\circ$ until the evolution of nitrogen ceased. The solid mass formed after cooling was dissolved in alkali and neutralized by the addition of solid carbon dioxide, and the precipitate which deposited was separated off. The yield was 15 g (50%), m.p. $127-129^\circ$ (from ligroin). Addition product with phenyl isocyanate: m.p. $117-118^\circ$.

Found %: C 62.45, 62.62; H 5.95, 5.99. $\text{C}_{23}\text{H}_{25}\text{O}_6\text{N}_3$. Calculated %: C 62.86; H 5.73.

The 3-aryl-1,4,5,6-tetrahydropyridazines were obtained by the hydrolysis and decarboxylation of the corresponding 1,2-diethoxycarbonyl-3-aryl-1,2,3,6-tetrahydropyridazines with alcoholic alkali by a reported method [1].

3-*p*-Nitrophenyl-1,4,5,6-tetrahydropyridazine (IV), obtained from (I) with a yield of 43%, was purified by dissolution in hydrochloric acid (1 : 1) with subsequent precipitation by solid sodium acetate and washing with water; m.p. $124-126^\circ$ (decomp.).

Found %: C 58.94, 58.89; H 5.38, 5.23. $\text{C}_{10}\text{H}_{11}\text{O}_2\text{N}_3$. Calculated %: C 58.53; H 5.40

3-*p*-Aminophenyl-1,4,5,6-tetrahydropyridazine (V), was obtained from substance (II). The yield was 43%, m.p. $126.0-126.5^\circ$ (from aqueous alcohol). Reaction product with phenyl isothiocyanate: m.p. $157-158^\circ$ (from a mixture of acetone and ligroin).

Found %: C 64.14, 64.29; H 5.16, 4.91. $\text{C}_{24}\text{H}_{25}\text{N}_5\text{S}_2$. Calculated %: C 64.59; H 5.20.

* With the participation of L. Dorofeeva.

3-*p*-Hydroxyphenyl-1,4,5,6-tetrahydropyridazine (VI), was obtained from substance (III). The yield was 52%, m.p. 225-226° (from water).

Found %: C 67.82, 67.78; H 6.72, 6.63. $C_{10}H_{12}ON_2$. Calculated %: C 68.16; H 6.86.

Behavior of para-substituted 3-aryl-1,4,5,6-tetrahydropyridazines in catalytic decomposition. 3-*p*-hydroxyphenyltetrahydropyridazine (VI). To a Wurtz flask were added 5 g (0.028 mole) of substance (VI), 1.7 g (0.030 mole) of caustic potash, and 0.5 g of platinum on activated carbon; the mixture was heated until the evolution of gas ceased (400-450°). The catalyzate was dissolved in 2 N caustic potash and the solution was acidified with concentrated hydrochloric acid to an acid reaction, and neutralized with aqueous ammonia. The precipitate which separated was filtered off with suction and subjected to vacuum sublimation. The yield was 2.7 g (55%), m.p. 225-226°. Literature data [4]: m.p. 227°. The gas evolved consisted solely of hydrogen.

3-*p*-Aminophenyltetrahydropyridazine (V) was decomposed by the usual method [1]. The gas evolved was analyzed (it consisted of hydrogen, saturated and unsaturated hydrocarbons, and nitrogen, and did not contain methane). The catalyzate was dissolved in ether and the solution was extracted with 2 N hydrochloric acid, the hydrochloric acid solution was neutralized with 2 N caustic soda and extracted with ether. The ethereal extracts were dried with magnesium sulfate. The ether was distilled off and the residue subjected to fractional distillation *in vacuo*.

1st fraction - *p*-ethylaniline (yield 32%), b.p. 94-95° (10 mm), n_D^{20} 1.5587, d_4^{20} 0.9952, M_R^{20} 39.30. $C_{10}H_{11}N$. Calculated 38.97. Literature data [5]: b.p. 213-214° (760 mm), n_D^{20} 1.5529, d_4^{20} 0.9751. Addition product with phenyl isothiocyanate (*N*-phenyl-*N'*-*p*-ethylphenylthiourea), m.p. 136-137° (from alcohol).

Found %: C 70.13, 70.30; H 6.15, 6.29; N 10.62, 10.73. $C_{15}H_{16}N_2S$. Calculated %: C 70.27; H 6.29; N 10.93.

A mixed melting point test with the thiourea derivative obtained from specially synthesized *p*-ethylaniline* showed no depression of the melting point.

2nd fraction - *p*-aminophenylcyclobutane (yield 13%), b.p. 129-132° (10 mm), n_D^{20} 1.4758, d_4^{20} 1.0342. Literature data [3]: b.p. 129-130° (10 mm) n_D^{20} 1.4806, d_4^{20} 1.0373. Addition product with phenyl isothiocyanate: m.p. 138-139° (from alcohol). A mixed melting point test with the thiourea from authentic aminophenylcyclobutane obtained by the reduction of the corresponding nitro compound [3] showed no depression of the melting point.

Distillation residue - *p*-aminophenylpyridazine (yield 55%), m.p. 146-147° (from aqueous alcohol). Its structure was shown by conversion to 3-phenyl- and 3-*p*-hydroxyphenylpyridazines.

Elimination of the amino group by the diazo reaction yielded 3-phenylpyridazine (yield 46%), m.p. 100-101° (from alcohol). Literature data [6]: m.p. 102-103°. A mixed melting point test with authentic 3-phenylpyridazine obtained by the sulfur dehydrogenation at 350° of 3-phenyl-1,4,5,6-tetrahydropyridazine in a yield of 75% showed no depression of the melting point.

Replacing the amino group of 3-*p*-aminophenylpyridazine by the hydroxyl group by means of the diazo reaction gave 3-*p*-hydroxyphenylpyridazine (yield 61%, purified by vacuum sublimation, m.p. 225-226°), which proved to be identical with the preparation obtained from hydroxyphenyltetrahydropyridazine (see above).

3-*p*-Nitrophenyl-1,4,5,6-tetrahydropyridazine (IV) was decomposed by the same method as for the aminophenyltetrahydropyridazine, but on heating to ~500°. The gas evolved consisted solely of hydrogen.

1st fraction - aniline (yield 23%), b.p. 85-86° (10 mm), n_D^{20} 1.5845, d_4^{20} 1.2187. Thiourea derivative formed with phenyl isothiocyanate m.p. 164-165° (from a mixture of ligroin and acetone).

Found %: C 69.06, 68.93; H 5.45, 5.51; N 12.29, 12.47. $C_{15}H_{12}N_2S$. Calculated %: C 68.82; H 5.30; N 12.27.

A mixed melting point test with a preparation obtained from aniline showed no depression of the melting point.

2nd fraction - (yield 5%, not further investigated), b.p. 190° (2 mm), m.p. 78-79° (from ligroin).

Found %: C 70.79, 70.90; H 6.09, 6.03; N 18.02, 18.23. $C_{10}H_{10}ON_4$. Calculated %: C 70.56; H 5.92; N 18.29.

SUMMARY

1. Under the conditions of catalytic decomposition at 400-450°, 3-*p*-hydroxyphenyl-1,4,5,6-tetrahydropyridazine does not decompose by the usual route with the formation of arylcyclobutane and the corresponding styrene, but undergoes dehydrogenation to 3-*p*-hydroxyphenylpyridazine.

* Made by heating aniline and alcohol in an autoclave in the presence of zinc chloride [6].

2. 3-p-Aminophenyl-1,4,5,6-tetrahydropyridazine also dehydrates on decomposition but, in addition to this, it also undergoes decomposition with the formation of aminophenylcyclobutane and p-aminophenylethylene, which hydrogenates during the reaction.

3. The decomposition of 3-p-nitrophenyl-1,4,5,6-tetrahydropyridazine, which commences only at a temperature of about 500°, is accompanied by dehydrogenation and far-reaching degradation.

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INVESTIGATION IN THE FIELD OF SULFOXIDES AND SULFONES

II. THE STEREOCHEMISTRY OF THE ADDITION OF THIOLS TO THE TRIPLE BONDS OF DIACETYLENE AND 1-ALKYLTHIOBUT-1-EN-3-INES AND THE PROPERTIES OF THE ISOMERIC 1,4-DIALKYLTHIOBUT-1,3-DIENES*

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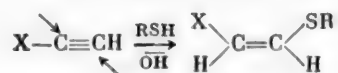
pp. 2487-2496, August, 1961

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It has been shown in early investigations [1, 2] that thiols readily add to one of the triple bonds of diacetylene (I) in the presence of catalytic amounts of alkali, and that this reaction is not accelerated by free-radical initiators and is not inhibited by antioxidants. It was therefore concluded that it bore the character of an ionic nucleophilic addition. It was further established that the addition of a second molecule of thiol to a 1-alkylthiobut-3-en-1-ine (II) with the formation of 1,4-dialkylthiobut-1,3-dienes (III) required considerably more severe conditions. This reaction is not accelerated by catalytic amounts of alkaline catalysts and requires heating and the presence of free-radical initiators (oxygen, diniiz) and is inhibited by antioxidants (hydroquinone, triethylamine, SO_2), i.e., it bears the character of a free-radical addition and not an ionic one [1, 3].

It was of interest to investigate the stereochemistry of these two reactions, the more so since the stereochemistry of addition reactions to triple bonds in diacetylene or vinylacetylene systems has not been studied at all, although there are isolated indications of the formation, as the result of such reactions, of mixtures of stereoisomeric butadienes [3, 4]. Diacetylene and ethinyl vinyl sulfide add thiols in the 1,2-position to one of the acetylenic bonds, which allows them to be considered not as typical conjugated systems but as mono-substituted acetylenes and the search for literature analogs to be made in this direction.

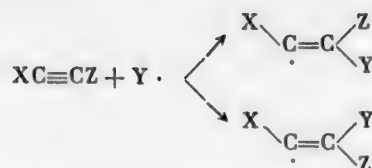
It has been shown in the last five years [5, 7] that for mono-substituted acetylenes with electron-acceptor substituent groups, the reaction of ionic nucleophilic addition of thiols obeys "the rule of trans addition" practically without exception. As a result of the stereospecificity of the reaction, 1,2-disubstituted ethylenes with a cis structure are formed.



It was established in this connection [8] that activation of the triple bond to nucleophilic attack increases in the following sequence together with the increase in the electron-acceptor properties of the substituent X: $\text{X} = \text{ArS} < \text{Cl} < \text{C}_6\text{H}_5 < \text{CO}_2 < \text{CO}_2\text{R} < \text{COAr}$.

The stereochemistry of the addition of thiols to triple bonds under free-radical conditions has not been studied. However, from results relating to other free-radical reactions of acetylenes, it may be concluded that, under these conditions, acetylene systems differ fundamentally from ethylene systems. For ethylene compounds, as has recently been shown [9], both heterolytic and homolytic addition reactions frequently obey the rule of trans addition of the residues. For acetylenes, however, the stereochemistry of the final products of the homolytic reaction is apparently determined by the relative efficiency of the formation, and hence of the different stabilities of, the "ethylene-like" free radicals arising as intermediates [10, 11].

* Previous communication on the investigation, see ZhOKh 30, 3143 (1960).

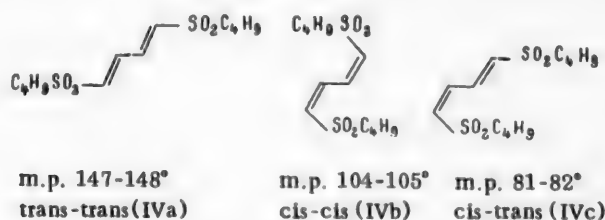


This stability depends on the ratio of the mutual forces of repulsion between the entering group and the unpaired electron of the double bond, on the one hand, and of the same group and the substituents on the acetylene bond, on the other hand. Hence, different cases are possible in free-radical addition to a triple bond. Thus, in the investigations [11], it was found that the free-radical hydrobromination of bromoacetylenes ($Y = X = Br$; $Z = Alk$) goes with stereospecific *cis* addition of the residues. At the same time, it has been shown [12] that methylacetylene hydrobrominates under homolytic conditions stereospecifically with *trans* addition of the residues. The free-radical bromination of mono- and dialkyl acetylenes goes non-stereospecifically with the formation of mixtures of products, the structure of which depends on the nature of the substituents Y and Z [10, 11]. Under ionic conditions, all these reactions are stereospecific and follow the rule of *trans* addition [9-12] which, probably, is an indication of the fact that they take place through the formation of a " π complex" and not in two stages with the formation of intermediate carbonium ions.

The literature data cited above must also be borne in mind when approaching the study of the stereochemical relationships in the reaction which interests us, for which we selected diacetylene and butanethiol as reactants. Diacetylene adds thiols exothermically in the presence of traces of alkali; thus, the second ethynyl group enters into relationship with the one which adds as a strong electron-acceptor substituent which must be placed in the right-hand part of the sequence given above. As was to be expected, this reaction proved to be stereospecific. In fact, we found that the 1-butylthiobut-1-en-3-ine (II) obtained, on the action of an alkaline mercury reagent, gives a quantitative yield of the mercury bisacetylide $Hg(C\equiv C-CH=CHSC_4H_9)_2$ with a sharp m.p. of $115-115.2^\circ$ not changing after a number of recrystallizations. Although we did not demonstrate this specially, compound (II) must be assigned the *cis* structure not only on the basis of the principle of *trans* addition (by analogy with other cases of nucleophilic addition); the *cis* structure (II) follows without question from the structure of the dibutylthiobutadienes (III) formed in the reaction of (II) with butane thiol, which we have carefully demonstrated.

We carried out the reaction of (II) with butanethiol under very diverse conditions, and converted the compounds (III) formed into the crystalline sulfones (IV) by oxidation with acetyl peroxide in ethereal solution at low temperatures ($+5, -5^\circ$), which excluded the possibility of their isomerization, and then separated the mixture of sulfones (IV) by fractional precipitation from dioxane with water. The method of separation used, again, could not lead to isomerization of the sulfones.

We obtained in individual form all three possible isomers of 1,4-dibutylsulfonylbuta-1,3-diene (IVa, b, c).



The structure ascribed to these compounds was confirmed by the following facts.

(1) The melting point falls from the *trans-trans* through the *cis-cis* to the *cis*-isomer, i.e., it follows the same course as in the case of other 1,4-disubstituted buta-1,3-dienes where the structure of the isomers has been shown, namely diphenyl- [13] and diacetoxybutadienes [14].

(2) The *trans-trans* configuration (IVa) is confirmed by the fact that it is formed quantitatively from (IVb) and (IVc) when they are isomerized in the presence of iodine in diffused light, which, for compounds with a polyene structure, leads, as is well known, [13], to the production of up to 98% of the *trans-trans* form.

(3) All the compounds obtained have an absorption maximum in the ultraviolet spectra* at 240-243 m μ , the intensity of the absorption falling from (IVa) through (IVb) to (IVc) (see Figure), i.e., in the same order in which the intensities of the spectra of other 1,4-disubstituted butadienes change [12,13]. It is well known that, in a series of 1,2-substituted ethylenes, the trans compounds always absorb more intensively in the ultraviolet than the cis compounds.

(4) The infrared spectra of (IVa, b and c) are characterized by a large number of absorption bands, which make their analysis difficult. In the spectrum of (IVa), however, (see Table 1) the greatest intensity is characteristic of the C-H "trans" band (978 cm⁻¹), for (IVb) it is characteristic for the C-H "cis" band (766 cm⁻¹), and in the spectrum of the isomer (IVc) both these frequencies are present with a fair intensity. In addition, (IVb and c) have a common band at 870-880 cm⁻¹, absent from the spectrum of (IVa) and, obviously, also characteristic of isomers containing a cis C-H bond. The frequency of the band corresponding to the vibrations of the C=C bond is somewhat higher for (IVa) and lower for (IVb and c) which also corresponds to what would be expected.

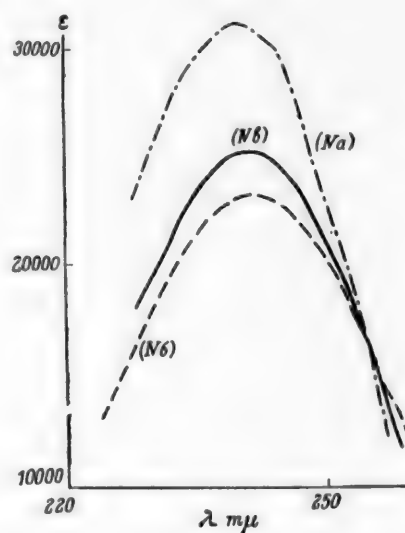
(5) Finally, the cis-trans structure of (IVc) is shown also by the fact that this isomer has a considerably higher dipole moment (5.19D) than (IVa) and (IVb), which have 4.11 and 4.19 D, respectively. This is to be expected if one considers that all these substances must have the "S-trans" conformation which has been shown for a large number of substituted butadienes [15]. The unsuitability of the "S-cis" configuration in this case is confirmed also by the construction of molecular models of (IVa, b and c).

TABLE 1. Absorption bands for the Isomers (IVa, b and c) Differing in Frequency or Intensity*

(IVa)	(IVb)	(IVc)
1580 (med.)	1558 (med.)	1560 (med.)
978 (med.)	981 (weak)	989 (med.)
-	870 (med.)	888 (med.)
752 (weak)	766 (strong)	766 (med.)

* The spectra of compounds (IV) contain a large number of bands agreeing in intensity and frequency, in particular, the intense bands of the SO₂ group at 1313, 1279, and 1129 cm⁻¹.

We separated the mixture of isomeric substances (IV) obtained from the addition products of butanethiol to (II) under very diverse conditions (Table 2). We succeeded in carrying out a stereospecific ionic addition of the thiol to (II) with the formation of practically pure cis-cis (IIIb) (experiment 15) - in complete agreement with the principle of trans addition. To attain this, it is necessary to exclude air from the reaction medium as completely as possible (evacuated tube, inhibitor), to convert the whole of the thiol into the thiolate, and to heat the reaction mixture for a long time in ethanol. A small amount of (IVc) (5-8%) in the sulfone obtained on the oxidation of the reaction products in this procedure is evidently due to isomerization (IIIb→IIIc) during the protracted heating. On the other hand, carrying out the reaction under conditions favoring free-radical addition: with free thiol, in the presence of air, and with dilution by an inert solvent, we obtained, although in small yield, a mixture of (IIIb) and (IIIc) with (IIIc) predominating (experiment 13). A specially undertaken experiment (see Table 3) showed that, under these conditions, (IIIc) partially isomerizes into (IIIb) (most probably under the action of heat and oxygen); however, after attempts at isomerization, the ratio of IIIc to IIIb remained about 6 : 4. Thus, free-radical addition of butanethiol to (II) does not go stereospecifically, cis addition predominating in this case. If the reaction is carried out under conditions of competition between free-radical and ionic conditions (experiment 6 - simultaneous presence of free thiol, thiolate, and atmospheric oxygen), then the reaction goes slowly and, judging from the composition of the products, mainly by the free-radical route. Under these conditions, (IIIa)



Ultraviolet spectra of the sulfones. The symbols on the curves correspond to the numbers of the compounds.

* The UV absorption spectra were measured by G. Andrianova, the IR spectra by A.P. Simonov, and the dipole moments by A.F. Gol'dshtein and E.N. Gur'yanova, to whom we express our thanks.

TABLE 2. Composition of the Mixtures of Sulfones (IV) Obtained by Oxidizing (III) Synthesized Under Various Conditions [0.05-0.025 g-mole of (II) were used in the reactions]

Exp. No.	Conditions of the synthesis of (III)				Yield of (III) in (%)	Yield of mixture of sulfones (IV) (in %)	M.p. of (IV) before fractionation	Composition of the mix. of (IV) in % from the results of frac.		
	Catalyst	Reagent B added	Molar ratio of (II) to (B)	Temperature of heating	Total time of heating (hr)			(IVa)	(IVb)	(IVc)
15	Na ethoxide (inhibitor, phenyl- <i>a</i> -naphthylamine)	Na butylthiolate (in anhydrous alcohol)	1:1.25	80°	50	80-87	95-97	1-1st fraction 101-103° 2-2nd fraction 82-96**	—	92-95 5-8
12	} Atmospheric oxygen	Butanethiol (in heptane)	1:1.5	60-70	14	25	45-60*	1-1st fraction 82-92 2-2nd fraction 80-85**	—	15-20 80-85
13		Butanethiol	1:3	65-60	12	26.4	44*	1-1st fraction 92-103 2-2nd fraction 80-92**	—	50 75
5		Butanethiol + butylthiolate	1:1	80-85	45	48.5	50*	96-110	5	15
6		Butanethiol	1:2	55-60	10	70	80	1-1st fraction 101-129 2-2nd fraction 80-101**	15	50 30
10	Dinitilz	Butanethiol	1:2	100-140	18	81.6	85.3	85-123	22	25 42
2	} Traces of oxygen	Butanethiol	1:2	40-50	186	50	70	1-1st fraction 88-120 2-2nd fraction 82-101**	10	20 55
3		Butanethiol	1:2	100-120	9	70	78	80-117	14	22 50
1	Traces of oxygen + 0.08 g of "Triton B"	Butanethiol	1:2	100-120	9	70	78	80-117	14	22 50

* These experiments were carried out with small amounts (0.4-0.5 g of the substance was taken for oxidation); the low yields are explained by losses on working up.

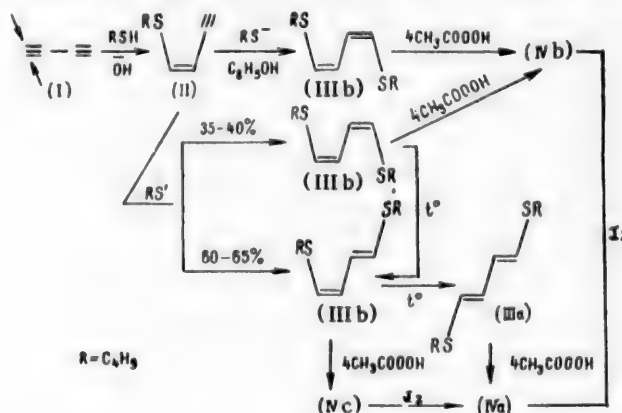
** The first fraction of crystals precipitated during the oxidations; the second fraction was isolated from the mother liquors after evaporating the ether and usually amounted to not more than 10-15% of the total amount of (IV).

TABLE 3. Isomerization of the Dithioethers (IIIb) and (IIIc)

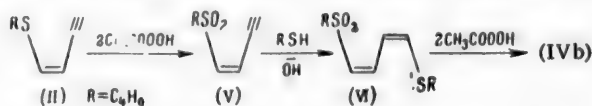
Composition of the dithioether used (in %)		Isomerization conditions	Yield of sulfone in % (total) after oxidation of the isomerizate	Composition of the mixture of sulfones, in % of the amounts obtained		
(IIIb)	(IIIc)			(IVa)	(IVb)	(IVc)
95	5	16 hours heating (60-70°) in heptane (flask with reflux condenser)	76	—	70	30
95	5	16 hours heating (110-120°) in heptane in a tube from which air had been evacuated (to 3-5 mm)	67	15	50	30
95	5	15 hours heating (80-90°) in the presence of 1% of diniiz, tube in atmosphere of air	96	—	30	70
15	85	Same conditions as in preceding experiment	90	30	15	50

appears in the reaction mixture, probably as a product of the isomerization of (IIIc). Adding diniiz to the reaction mixture (experiment 10) and raising the temperature (experiment 2) increase the overall rate of the reaction; however, thanks to the superimposition of processes of thermal and catalytic isomerization (IIIb→IIIc→IIa) (see also Table 3), it leads to confused mixtures of products, which do not permit any deductions at all to be made on the stereochemistry of the initial process. Adding the active anionic inhibitor "Triton B" (experiment 1) under these conditions did not change the composition of the reaction mixture.

The stereochemical relationship in the reactions studied may be represented by the following scheme:



Ionic addition with a fairly high stereospecificity can also be achieved by first oxidizing (II) to the corresponding sulfone (V) and then adding a molecule of the thiol to (V) in the presence of "Triton B". Oxidation of the reaction products leads to the production of (IVb) with a yield of approximately 25%, slightly contaminated with (IVc). In addition to these, a non-crystallizing oil, which gives a positive reaction for acetylenic hydrogen, is found.



Thus, we have shown that the stereochemistry of the 1,2 addition of thiols to a triple bond, both in diacetylene and vinyl ethynyl systems is apparently subject to the same laws as have been established for reactions of non-conjugated acetylenic bonds. The ionic reaction with nucleophilic alkylthiolates is stereospecific and follows "the rule of trans addition". Hence, it follows that an intermediate ion with the allene structure cannot be formed in this reaction, as has been proposed by Bohlmann et al. [16] to explain the course of some nucleophilic addition reactions of diacetylene. Under free-radical conditions, the thiol adds to the vinyl ethynyl system non-stereospecifically; this latter reaction takes place either by partial cis addition of the entering groups or by the partial isomerization of the intermediate free radicals [17].

EXPERIMENTAL

Di-(4-butylthiobut-3-en-1-in-1-yl)-mercury. 1-Butylthiobut-1-en-3-ine (II) was synthesized from diacetylene (I) and butanethiol in an excess of (I) dissolved in methyl alcohol [2] and had b.p. 72-72.5° at 3 mm, n_D^{20} 1.5260. To prepare the mercury derivative, 22.5 ml of an alkaline mercury reagent prepared according to [18] from 0.028 g-mole of $HgCl_2$ was added slowly dropwise with stirring and cooling with ice water to 2 g (0.014 g-mole) of (II) dissolved in 40 ml of ethanol. A copious white precipitate rapidly began to separate, which, after filtration, washing with 50% ethanol, and drying in the vacuum desiccator, weighed 3.15 g (93%). After recrystallization from alcohol it formed white leaflets with m.p. 115.0-115.2° (not changing after repeated recrystallization).

Found %: Hg 41.50; C 40.45; H 4.56. $C_{16}H_{22}S_2Hg$. Calculated %: Hg 41.90; C 40.11; H 4.62.

1,4-Dibutylthiobuta-1,3-dienes (IIIa, b, and c). The boiling points and refractive indices of some of the mixtures of isomeric substances (III) obtained under various conditions are given in Table 4 (see also Table 2).

TABLE 4. Properties of Mixtures of the Dithioethers (III)

Exp. No.	B.p. (pressure in mm)	n_D^{20}	Composition of the mixture (see Table 2)
1	169-171° (2)	1.5680	140% (IIIa) + 220% (IIIb) + 500% (IIIc)
2	92-97 (0.03)	1.5670	220% (IIIa) + 250% (IIIb) + 400% (IIIc)
6	78-90 (0.004)	1.5615	50% (IIIa) + 150% (IIIb) + 750% (IIIc)
10	107-110 (0.04)	1.5670	150% (IIIa) + 500% (IIIb) + 300% (IIIc)
13	99-104 (0.03)	1.5620	— 200% (IIIb) + 800% (IIIc)
15	97-102 (0.05)	1.5660	— 950% (IIIb) + 50% (IIIc)

Experiments 1, 2, and 15 (Table 4) were carried out in sealed tubes from which the air had been evacuated after the introduction of the reactants, experiment 10 was carried out in an atmosphere of air, experiment 6 in a flask with a reflux condenser in a current of nitrogen, and experiment 13 in a flask with a reflux condenser in an atmosphere of air. Cis-trans-(IIIc) possesses the lowest refractive index (n_D^{20} 1.5580-1.5600), then come (IIIb) (n_D^{20} 1.5660-1.5670) and (IIIa) (n_D^{20} 1.5680).

Experiments were also carried out on the synthesis of (III) directly from (I) and butanethiol, without the isolation of (II). For this, 11 g of (I) were dissolved with cooling to -10--15° in 50 ml of butanethiol containing 0.5 g of NaOH (current of nitrogen). The reaction mixture was allowed to stand at 0° for 1 hour and was then kept at 50-55° for 5 hours. The excess of thiol was distilled off from half the reaction mixture and this part of the product was distilled. Yields of 5.3 g of (II) [38%, calculated on (I)] and 4.6 g (20%) of (III) with b.p. 100-107° at 0.03 mm, n_D^{20} 1.5620 (sulfone m.p. 86-90°) were obtained. The second half of the reaction mixture was heated in a sealed tube at 75-80° for 22 hours. Yields of 3.2 g (22.8%) of (II) and 7.0 g (30.4%) of (III), b.p. 92-102° at 0.015 mm, n_D^{20} 1.5600 (sulfone m.p. 86-96° - a mixture of IIIb + IIIc) were obtained.

Oxidation of mixtures of (IIIa, b, and c) to (IVa, b and c). In all experiments, the oxidation was carried out under the same conditions - with the theoretical quantity of concentrated peracetic acid in ether.

Experiment 1. A solution of 6.5 g (0.028 mole) of (III) in 50 ml of ether was prepared and 13 g of 72% CH_3COOH was added with stirring and cooling at such a rate that the temperature of the reaction did not exceed +5°. After 30 min, the separation of crystals of (IV) began. Stirring was continued for another hour, after which the mixture was left for 3 days at room temperature. The crystals were filtered off, washed on the filter with ether, and dried in the vacuum desiccator; weight 6.3 g, m.p. 80-117°. After evaporation of the ether and washing the acetic acid out of the mother liquors with water, a further 0.5 g of crystals, m.p. 82-92°, were obtained. The total yield of the mixture of sulfones (IVa, b and c) was 78%.

Found %: C 49.21; H 7.36; S 21.30. $C_{12}H_{22}O_4S_2$. Calculated %: C 48.95; H 7.58; S 21.73.

Fractional separation. The mixture of the sulfones (IVa, b and c) was dissolved in dioxane at the rate of 20-25 ml per 1 g, and was divided into 6-9 fractions by the gradual addition of small portions of water. After the addition

of each new portion of water, the solution was allowed to stand for 1-2 hours in a refrigerator or in ice water for more complete separation of the precipitates. Fractional precipitation was carried out repeatedly (8-10 times), until fractions with constant melting points were obtained. The results of the separation of the sulfones are given in Table 3.

(IVa): m.p. 147-148°; crystallizes from dioxane in the form of long needles. Found %: C 48.85; H 7.64; S 21.63.

(IVb): m.p. 104.105°; crystallizes from dioxane in the form of fine fibrous crystals. Found %: C 48.96; H 7.43; S 21.84.

(IVc): m.p. 81-82°, separates from dioxane in the form of an almost amorphous mass of fine crystals. Found %: C 49.21; H 7.64; S 21.62. $C_{12}H_{22}O_4S_2$. Calculated %: C 48.95; H 7.63; S 21.73.

The UV spectra were determined in ethanol solution (see Figure). Pastes with vaseline oil were used for the determination of the IR spectra. The determination was carried out on an IKS-14 double-beam apparatus (accuracy of the frequency determination $\pm 3 \text{ cm}^{-1}$).

Isomerization (IVb→IVa). A small crystal of iodine was added to 0.07 g of (IVb) dissolved in 2 ml of dioxane, and the solution was allowed to stand in sunlight. After two days, the precipitation of long needles of (IVa) began. The dioxane was removed *in vacuo*, and the crystals were washed with water. After filtration and drying, 0.06 g of (IVa) with m.p. 147-148°, not depressed in admixture with a sample of (IVa) obtained by the separation of mixtures of (IV) was obtained. The IR and UV spectra of (IVa) obtained by the various methods are identical.

Isomerization (IVc→IVa). This was carried out under the same conditions as the isomerization (IVb→IVa). A yield of 0.48 g of (IVa) with m.p. 147-148°, identical with that isolated from the mixture of sulfones, was obtained from 0.59 g of (IVc).

1-Butylsulfonylbut-1-en-3-ine (V). Seven grams of (II) were dissolved in 100 ml of dry ether and oxidized with 9 g of 86% CH_3COOOH , with cooling. The oxidation product was worked up after 9 days. The reaction mixture was diluted with ether to 500 ml, after which a precipitate of a polymer of (V) separated (weight 0.4 g). To the solution was added 11 g of anhydrous NaHCO_3 , and it was kept for 1 day, with stirring, to neutralize the acid, after which the ether was removed *in vacuo*. After distillation, 3.5 g of (V) was obtained. Yield 40%.

B.p. 78-79° at 0.03 mm, 88-91° at 0.04 mm, n_D^{20} 1.5022, d_4^{20} 1.1020, M_{rD} 44.6; calc. 45.17.

Found %: C 55.52; H 7.23; S 18.33. $C_8H_{12}O_2S$. Calculated %: C 55.81; H 6.98; S 18.61.

The substance (V) can be kept only in tubes under nitrogen; in air it rapidly polymerizes and resinifies.

After distillation of (V) 4 g of a dark resinous residue remained in the flask; by solution in dioxane and precipitation with ether, this yielded 2 g of yellow pulverulent polymer, the analysis of which showed that the polymerization of (V) is accompanied by oxidation.

Found %: C 53.26; H 6.91; S 17.94. $(C_8H_{12}O_2S)_n$. Calculated %: C 55.81; H 6.98; S 18.61.

(IVb) from (V). To 3.1 g of (V) (0.018 mole), 3.3 g (0.036 mole) of butanethiol was added in a current of nitrogen (flask with stirrer), after which 4 drops of "Triton B" in the form of a 40% aqueous solution was added (cooling with ice water). The external cooling was removed, and the temperature gradually rose to +27°. The mixture was allowed to stand overnight. After removing the excess of thiol, 2.3 g of a dark-colored addition product (VI) with b.p. 144-148° at 0.025 mm (50%) was distilled from the reaction mixture. A solution of 2.0 g of this substance dissolved in 10 ml of ether was oxidized under the conditions described above with 2 ml of 86% CH_3COOOH . After working up the mixture, 0.49 g (22%) of crystals of (IVb) with m.p. 95-100°, which, after reprecipitation from a mixture of dioxane and water, had m.p. 101-102°, were obtained. In addition, 1.08 g of a viscous non-crystallizing oil, giving a positive reaction with an alkaline mercury reagent for the presence of acetylenic hydrogen, was isolated from the reaction mixture.

SUMMARY

1. It has been shown that the 1,2-addition of a thiol to diacetylene and a 1-alkylthiobut-1-en-3-ine under ionic nucleophilic conditions proceeds stereospecifically with the formation of the corresponding *cis* products, i.e., the rule of *trans* addition is followed.

* The melting point of (IVc) can only be determined rapidly by immersing the capillary in the pre-heated apparatus; on slow melting, isomerization takes place, as a result of which the melting point is extended.

2. Under the conditions of free-radical addition of the thiol, a non-stereospecific reaction is found with the formation, mainly, of the cis-trans-butadiene dithioether, together with a small amount of the cis-cis product. It has been shown that in the presence of air and at high temperatures, secondary isomerization reactions are superimposed which distort the initial stereochemistry of the process.

3. The stereoisomeric forms of the 1,4-dibutylsulfonylbuta-1,3-dienes have been isolated and their geometrical configuration has been shown.

4. 1-Butylsulfonylbut-1-en-3-ine has been synthesized and it has been shown that the addition of butanethiol to it in the presence of "Triton B" goes stereospecifically with respect to the triple bond, with the formation of the cis-cis product.

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INVESTIGATIONS IN THE FIELD OF SULFONES AND SULFOXIDES

III. THE COMPARATIVE REACTIVITY OF α,β -NON-SUBSTITUTED SULFOXIDES AND SULFONES WITH RESPECT TO NUCLEOPHILIC REAGENTS

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Vinyl alkyl sulfoxides represent the simplest group of α,β -unsubstituted sulfoxides in which the mutual influence of a double bond and the sulfonyl group emerges particularly clearly. An investigation of the nature of a sulfide group having simultaneously a strong electron-acceptor (an oxygen atom) and a pair of free electrons capable of giving rise to electron-donor properties (for example, by forming thionium compounds with alkyl halides [1]) on the sulfur atom is of undoubted interest. These properties of conflicting nature probably also make the sulfoxides unstable, to a certain degree, and readily capable of giving up their oxygen (this property being employed, for example, for oxidation under very mild conditions using dimethyl sulfoxide [2]).

Some information on reactions of substituted aryl vinyl sulfoxides and higher alkyl vinyl sulfoxides - of the type of vinyl octadecyl sulfoxide - is contained in patents [3]. It has been shown that, in the presence of sodium ethoxide and on long boiling, thiols and hydrogen sulfide add to them, sulfinic acids readily react in the presence of alkalis, and sodium bisulfite, ammonia, and primary and secondary amines also readily react. Among these results, there is also an indication that thiocresol adds to vinyl ethyl sulfoxide on heating to 100° for 15 hours (sodium methoxide). The yield is not indicated. In all cases, it is reported that compounds of type of $\text{RSOCH}_2\text{CH}_2\text{X}$ are formed and that the addition reaction to vinyl sulfoxides goes rather less energetically than to the corresponding sulfones. It has been found [4] that divinyl sulfoxide does not react with thiophenol, ammonia, or phenylhydrazine without a catalyst, but that in the presence of alkoxides, it adds methanol and ethanol (reaction conditions and yields of products not given). More recently [5] it has been shown that divinyl and phenyl vinyl sulfoxides react exothermically with thiophenol in the presence of catalytic amounts of triethylamine and, in the presence of sodium bicarbonate, add mercaptoacids (thioglycolic, *o*-mercaptobenzoic) and mercaptoaminoacids of the type of cysteine, in the latter case addition taking place exclusively through the mercapto group. It is also shown in these papers that unsaturated sulfoxides are somewhat less reactive than the corresponding sulfones. Thus, there are no systematic investigations whatever in the literature of the reactivity of the simplest vinyl alkyl sulfoxides with respect to the simplest nucleophilic reagents under conditions permitting a comparison of them with the corresponding vinyl sulfones.

In the present work, this investigation is performed on the basis of the reactions of vinyl ethyl (I) and butyl (II) sulfoxides and vinyl ethyl sulfone (III) with alcohols (ethanol, propanol, butanol) and thiols (ethane-, propane-, and butanethiols, and thiophenol). "Triton B" (trimethylbenzylammonium hydroxide) was used as catalyst, as this, as we have shown previously [6], brings about a quantitative addition of alcohols and thiols to vinyl ethyl sulfone (III). Comparative results are given in Tables 1 and 2, a comparison of which shows that the sulfoxides are considerably less reactive with respect to nucleophilic reagents than the sulfones. Thus they require larger amounts of catalyst to produce a satisfactory yield and, even in the case of the addition of thiols the ions of which are distinguished by a highly nucleophilic character, the yield of addition product is considerably lower. These differences appear particularly sharply with respect to alcohols: while the sulfones add them exothermically with high yields, sulfoxides require long heating, (I) proving considerably less reactive than (II). The ease of addition of alcohols diminishes together with the nucleophilic character of the corresponding alkoxide ions: $\text{OC}_2\text{H}_5 \geq \text{OC}_3\text{H}_7 > \text{OC}_4\text{H}_9$.

A specially arranged experiment showed that (I), like (III) [6], has no tendency to the free-radical addition of thiols, since heating (I) with butanethiol for 12 hours at 50-55° in the presence of 1% of diniiz led to the production

of 1-ethylsulfinyl-2-butylthioethane with a yield less than 10%, and on allowing an equimolar mixture of the reactants to stand in air in the absence of any specially added catalyst, after 15 days practically no reaction whatever was observed. These results agree with the known [7] low values of the factor Q (characterizing the reactivity of a double bond with respect to a free-radical) found in the copolymerization of vinyl methyl sulfoxide with styrene and methyl methacrylate.

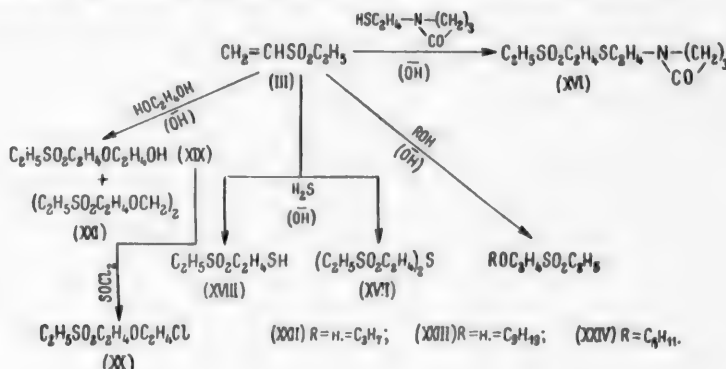
We also tested whether small amounts of the compounds formed "in accordance with Markovnikov's rule" were not, nevertheless, present in the products of the reaction of thiols to vinyl sulfoxides. For this purpose, the products of the reaction of (I) with ethanethiol were subjected to exhaustive oxidation with potassium permanganate.



1,2-Bis-(ethylsulfonyl)-ethane was obtained as the sole product and no trace of the lower-melting 1,1-bis-(ethylsulfonyl)-ethane was found.

All the compounds obtained from (I) and (II) - compounds IV-XV in Table 3 - are readily soluble in water, benzene, chloroform, alcohol, etc., but sparingly soluble in petroleum ether and heptane, and slightly more soluble in ether. The analogous compounds with an SO_2 group are considerably less soluble in water. The solubility can be changed over a fairly wide range by varying R and R'. All crystalline products were purified by recrystallization from boiling heptane. At room temperature, compounds of the type $\text{RSOCH}_2\text{CH}_2\text{XR}'$ are completely stable; however, they begin to decompose on heating above 120-130°, which (see note to Table 3) is strongly affected by their purity.

In this communication we shall give some information on certain addition reactions to vinyl ethyl sulfone (III) with the formation of compounds (XVI-XXIV) which we have not reported before or only very briefly [6a]; this information again confirms the high reactivity of (III) with respect to nucleophilic reagents.



EXPERIMENTAL

Vinyl ethyl sulfone (III) and vinyl ethyl (I) and butyl sulfoxides (II) were synthesized as described earlier [6, 9]. The properties of the products obtained from vinyl ethyl sulfone and ethanol, thiophenol [6a], butanol, and ethane-, propane-, and butanethiols [6b] have been reported earlier.

The 1-ethyl- and 1-butyl-sulfinyl-2-alkoxyethanes (IV-VII) were obtained from (I)/or(II)(0.025-0.1 mole) in equimolecular mixture with the corresponding alcohol (in some cases, a two-fold excess of the alcohol was taken). On adding the catalyst, a ~40% aqueous solution of "Triton B"*, no rise in the temperature was observed, in contrast to the reaction under the same conditions between the alcohols and (III) (see below and also [6]). The reaction mixtures were heated in sealed tubes (see Table 1), after which the products were isolated either by distillation from a flask with a short fractionating column (IV) or by distillation in a vacuum of 10^{-2} mm with preliminary freezing-out (V-VII). In the latter case, the reaction mixture was first freed by distillation *in vacuo* at room temperature from unreacted alcohol (2-3 mm) and sulfoxide (10^{-2} mm). After this, 0.7 ml of freshly-distilled ether was added for each gram of the reaction product; the mixture was cooled with ice water or dry ice and acetone until freezing began and was rapidly pressed out with continuous suction with filter sticks fitted with No. 3 glass filters [10]. The dry crystals were again mixed with a small portion of ether and the operation of sucking of the liquid was repeated. Then the substance

* The concentration of catalyst was determined by titrating a sample with 0.1 N HCl in the presence of methyl orange.

TABLE 1. Reaction with Alcohols (catalyst "Triton B").

R'	$\text{C}_2\text{H}_5\text{SO}_3\text{CH}_3$ (III) *				$\text{C}_4\text{H}_9\text{SO}_3\text{CH}_3$ (I)				$\text{C}_6\text{H}_{13}\text{SO}_3\text{CH}_3$ (II)			
	Reaction conditions				Reaction conditions				Reaction conditions			
	Catalyst [in moles-% on (III) etc.]	Temperature	Time (hours)	Yield (%)	Time of heating (hr)	Temperature	Time of heating (hours)	Yield (%)	Catalyst [in moles-% on (III) etc.]	Temperature	Time of heating (hr)	Yield (%)
C_2H_5	0.4	Room	24	91	1.6	55-65°	36	—	1.6	55-56°	36	50.3
$n\text{-C}_3\text{H}_7$	0.4	Room	24	87	1.6	100	48	50.5	1.6	80	40	57.4
$n\text{-C}_4\text{H}_9$	0.4	Room	24	89	1.6	55-65	36	—	1.6	55-65	36	52
					1.6	55-65	36	—	1.6	80	40	62
					1.6	100	48	—	1.6	55-65	36	52
										100	48	52

* Reaction with (III) exothermic after mixing the reactants and adding the catalyst.

TABLE 2. Reaction with Thiols (catalyst "Triton B").

R'	$\text{C}_2\text{H}_5\text{SO}_3\text{CH}_3$ (III) *				$\text{C}_4\text{H}_9\text{SO}_3\text{CH}_3$ (I) *				$\text{C}_6\text{H}_{13}\text{SO}_3\text{CH}_3$ (II) *			
	Reaction conditions				Reaction conditions				Reaction conditions			
	Catalyst [in moles-% on (III) etc.]	Temperature	Time (hours)	Yield (%)	Time of heating (hr)	Temperature	Time of heating (hours)	Yield (%)	Catalyst [in moles-% on (III) etc.]	Temperature	Time of heating (hr)	Yield (%)
C_2H_5	0.2	Room	24	86	1.6	50-55°	12	70-84	1.6	Room	48	81.0
$n\text{-C}_3\text{H}_7$	0.2	Room	24	99	0.8	Room	36	60.4				
$n\text{-C}_4\text{H}_9$	0.2	Room	24	96	1.6	50-55°	12	77.0	2.4	Room	48	81.0
C_6H_5	0.2	Room	24	90	1.6	50-55°	2 months	70.0	0.8	Room	48	65.2
					1.6	Room	24	62.0	1.6	Room	48	45.0
					1.6	Room	24	64.0				

* All reactions exothermic, except for the addition of $\text{C}_2\text{H}_5\text{SH}$ to (I).

TABLE 3. Properties of $\text{RSOCH}_2\text{CH}_2\text{OR}'$ and $\text{RSOCH}_2\text{CH}_2\text{SR}'$.

Compound No.	Formula	B.p. (pressure in mm)	Setting point	d_4^{20}	n_D^{20}	M_R		Found (%)			Calc. (%)		
						found	calc.	C	H	S	C	H	S
(IV)	$\text{C}_2\text{H}_5\text{SOCH}_2\text{CH}_2\text{OC}_2\text{H}_5$ **	109—110° (2)	44—45°	1.0544	1.4680	39.6	40.13	47.69	9.47	20.88	48.00	9.38	21.32
(V)	$\text{C}_4\text{H}_9\text{SOCH}_2\text{CH}_2\text{OC}_2\text{H}_5$	62—63 (0.02)	0	1.0002	1.4790	49.80	49.37	53.92	10.27	18.11	53.93	10.11	18.12
(VI)	$\text{C}_4\text{H}_9\text{SOCH}_2\text{CH}_2\text{OC}_3\text{H}_7$ n.	65—66 (0.02)	4.0—4.5	0.9797	1.4670	53.39	53.99	56.53	10.14	16.44	56.25	10.41	16.60
(VII)	$\text{C}_4\text{H}_9\text{SOCH}_2\text{CH}_2\text{OC}_4\text{H}_9$ n.	61.5—62.5 (0.03)	0.3—0	0.9659	1.4552	58.98	58.61	58.36	10.34	15.41	58.21	10.75	15.59
(VIII)	$\text{C}_2\text{H}_5\text{SOCH}_2\text{CH}_2\text{SC}_2\text{H}_5$	73—75 (0.03)	11—12	1.0852	1.5235	46.47	46.47	43.77	8.52	38.02	43.39	8.43	38.55
(IX)	$\text{C}_2\text{H}_5\text{SOCH}_2\text{CH}_2\text{SC}_3\text{H}_7$ n.	80—81 (0.009)	10	1.0707	1.5180	50.94	51.08	46.57	8.69	—	46.66	8.88	35.55
(X)	$\text{C}_2\text{H}_5\text{SOCH}_2\text{CH}_2\text{SC}_4\text{H}_9$ n.	64—65 (0.03)	21—22	1.0492	1.5125	55.46	55.70	49.23	9.57	32.60	49.49	9.27	33.00
(XI)	$\text{C}_2\text{H}_5\text{SOCH}_2\text{CH}_2\text{SC}_6\text{H}_5$	128—131 (0.02)	'M.p. 44-45	—	1.6125 ***	—	—	55.98	6.72	29.67	56.03	6.54	29.90
(XII)	$\text{C}_4\text{H}_9\text{SOCH}_2\text{CH}_2\text{SC}_2\text{H}_5$	96—99 (0.07)	23	1.0452	1.5110	55.71	55.70	49.14	9.34	32.67	49.49	9.27	33.0
(XIII)	$\text{C}_4\text{H}_9\text{SOCH}_2\text{CH}_2\text{SC}_3\text{H}_7$ n.	97 (0.03)	9—9.5	1.0292	1.5075	60.16	60.32	51.66	9.64	30.16	51.92	9.60	30.76
(XIV)	$\text{C}_4\text{H}_9\text{SOCH}_2\text{CH}_2\text{SC}_4\text{H}_9$ n.	93—96 (0.008)	10—11	1.6084	1.5040	65.25	64.94	53.73	10.10	28.53	54.05	9.90	28.86
(XV)	$\text{C}_4\text{H}_9\text{SOCH}_2\text{CH}_2\text{SC}_6\text{H}_5$	131—133 (0.02)	'M.p. 52-53	—	1.5740 ***	—	—	59.35	7.70	26.30	59.50	7.85	26.44

* The purification of the alkoxy- and alkylthio-alkylsulfonyl ethanes from contamination with the initial sulfoxide presented some difficulty. Crystalline substances gave good analyses immediately after a single recrystallization. Substance liquid at room temperature were purified by a single freezing-out and subsequent distillation at 10^{-4} mm. Distillation with a fractionating column could not be carried out at a higher pressure (2-3 mm) for substances boiling above $110-120^\circ$ at this pressure since, under these conditions, a considerable degree of decomposition commenced.

** Literature b.p. [8] 140° at 3 mm. No analytical data given. The other substances have not been reported before.

*** Determined immediately after distillation in the supercooled state.

was dried in a vacuum of 2-3 mm and distilled at 10^{-2} mm. The yields of products and their properties are given in Tables 1 and 3.

1-Ethyl- and 1-butyl-sulfinyl-2-alkyl- and -aryl-thioethanes (VIII-XV). These were obtained from (I) (or II) (0.025-0.1 g-mole) and an equimolecular amount of the thiol. In all experiments [except for the reaction of (I) with ethanethiol], after the addition of the catalyst a fairly considerable rise in temperature was observed although this was less than in the reaction of (III) with thiols. The products (VIII-X, XII, and XIII) were purified similarly to compounds to (IV-VII). Substances (XI) and (XV) set to a mass of crystals after the first distillation. After recrystallization from heptane they had the melting points shown in Table 3.

The oxidation of 1-ethylsulfinyl-2-ethylthioethane (VIII) was carried out in acetone solution with ice water cooling; KMnO_4 was added in portions with stirring and the calculated amount of sulfuric acid was also added in portions. Oxidation of 3 g of (VIII) (with b.p. $62-63^\circ$ at 0.03 mm) yielded 1.86 g (49%) of 1,2-bis-(ethylsulfonyl)-ethane with m.p. $137-138^\circ$, giving no depression of the melting point in admixture with a known sample [11].

1-Ethylsulfinyl-2-(β -N-pyrrolidonyl)-ethylthioethane (XVI). To a mixture of 3.6 g of (III) (0.032 g-mole) and 4.4 g (0.03 g-mole) of β -mercaptoethyl-N-pyrrolidone [12] was added 1 drop of "Triton B". The temperature rapidly rose to 70° , and then rapidly fell. On the next day, the reaction product was distilled. A yield of 5.9 g (74%) of (XVI) was obtained:

B.p. $185-187^\circ$ at 0.03 mm, n_D^{20} 1.5360, d_4^{20} 1.2489, MR_D 66.26; calc. 66.66, m.p. $35-3^\circ$.

Found %: C 45.06; H 7.27; S 23.98; N 5.03. $\text{C}_{10}\text{H}_{19}\text{O}_3\text{NS}_2$. Calculated %: C 45.26; H 7.22; S 24.16; N 5.28.

Bis-(ethylsulfonylethyl) sulfide (XVII) and 1-ethylsulfonyl-2-mercaptoethane (XVIII). In a tared tube fitted with a head-piece - a three-way cock with a gas-inlet tube - was placed 6 g (0.05 g-mole) of (III), the air was displaced from the tube with hydrogen sulfide, the lower part of the tube was immersed, in a current of hydrogen sulfide, in a vessel containing liquid nitrogen to condense the necessary amount of H_2S . The experiment was carried out under the conditions described earlier for the reaction of H_2S with vinyl alkyl ethers [13]. After the gas had been passed for 15 minutes, the tube was withdrawn from the Dewar vessel and disconnected from the gas supply system; 3 drops of the catalyst "Triton B" were added through the capillary for the introduction of H_2S and then the condensation was continued until 28 g of H_2S has been liquefied [0.8 g-mole or 16 moles per mole of (III)]. After this, the head-piece was connected with a vacuum rubber tube to a cock, the air was evacuated from the tube with continued liquid-nitrogen cooling, and the tube was sealed and placed in a vertical autoclave, into which nitrogen under a pressure of 15 atm was introduced to equalize the internal pressure. After 3 days, the tube was carefully removed from the autoclave (spectacles, gloves), cooled in liquid nitrogen, and opened, and the excess of hydrogen sulfide was evaporated from it. The solid amorphous residue obtained was repeatedly washed with benzene. The substance (XVII) insoluble in benzene was purified by precipitation from solution in chloroform with heptane. The yield was 4.85 g (67.9%), m.p. $108-109^\circ$.

Found %: C 35.25; H 6.79; S 34.82. $\text{C}_8\text{H}_{18}\text{O}_4\text{S}_3$. Calculated %: C 35.01; H 6.61; S 35.05.

The benzene solution was evaporated. On distilling the residue, 1.45 g (18.8%) of (XVIII) was obtained:

B.p. $86-88^\circ$ and 0.03 mm, d_4^{20} 1.2585, n_D^{20} 1.5110, MR_D 36.96; calc. 36.92. Found %: C 31.41; H 6.53; S 41.22. $\text{C}_4\text{H}_{10}\text{O}_2\text{S}_2$. Calculated %: C 31.14; H 6.54; S 41.58.

With a ratio of (III) to H_2S of 1 : 1, (XVII) was obtained with a yield of 85% and no (XVIII) was isolated at all.

1-Ethylsulfonyl-2-(2-hydroxyethoxy)-ethane (XIX), 1-ethylsulfonyl-2-(2-chloroethoxy)-ethane (XX), and 1,2-bis-(2-ethylsulfonylethoxy)-ethane (XXI). To a mixture of 6 g (0.5 g-mole) of (III) and 3.1 g (0.05 g-mole) of ethylene glycol, was added 3 drops of "Triton B". A rise in temperature was observed. The mixture was left for 3 days. On distillation 5.8 g (63.8%) of (XIX) was obtained:

B.p. $114-116^\circ$ at 0.03 mm, n_D^{20} 1.4371, d_4^{20} 1.2304, MR_D 41.60; calc. 41.64.

Found %: C 39.88; H 7.85; S 17.66. $\text{C}_8\text{H}_{14}\text{O}_5\text{S}$. Calculated %: C 39.54; H 7.74; S 17.60.

The residue after distillation was crystallized. The yield of (XXI) was 1.8 g (24%). After precipitating from chloroform with heptane, m.p. $56-57^\circ$.

Found %: C 39.55; H 7.30; S 21.19. $\text{C}_{10}\text{H}_{22}\text{O}_6\text{S}_2$. Calculated %: C 39.71; H 7.33; S 21.21.

Similarly, from 12 g (0.1 g-mole) of (III) and 3.1 g (0.05 g-mole) of ethylene glycol, 4.7 g (52.8%) of (XIX) and 6.5 g (43%) of (XXI) were obtained. To confirm the structure of (XIX), 3.6 g (0.02 g-mole) of it were treated in solution in 4 ml of anhydrous chloroform with 3 g (0.025 g-mole) of SOCl_2 in 1 ml of chloroform (flask with stirrer). After distilling off the chloroform and the excess of SOCl_2 , 2.7 g (68.6%) of (XX) was obtained:

B.p. 98° at 0.03 mm, n_D^{20} 1.4768, d_4^{20} 1.2632, M_{RD} 44.88; calc. 44.98.

Found %: C 35.77; H 6.39; S 15.73; Cl 17.43. $\text{C}_6\text{H}_{13}\text{O}_3\text{SCl}$. Calculated %: C 35.69; H 6.53; S 15.98; Cl 17.67.

1-Ethylsulfonyl-2-alkoxyethanes (XXII-XXIV) were obtained by mixing equivalent amounts of (III) and the appropriate alcohol. After adding 1-2 drops of the catalyst, pronounced heat-evolution was observed. The reaction mixture was cooled with ice water and the products were isolated after standing for some days.

(a) From 6 g (0.05 g-mole) of (III) and 3.5 g (0.57 g-mole) of propanol was obtained 7.8 g (87%) of (XXII):

B.p. $139-140^\circ$ at 5 mm, n_D^{20} 1.4508, d_4^{20} 1.0819, M_{RD} 44.95; calc. 44.73.

Found %: C 46.87; H 8.50; S 17.70. $\text{C}_7\text{H}_{16}\text{O}_3\text{S}$. Calculated %: C 46.76; H 8.92; S 17.74.

(b) From 6.6 g (0.055 g-mole) of (III) and 7.2 g (0.055 g-mole) of nonanol was obtained, after 2-fold distillation, 8.8 g (64.7%) of (XXIII) with b.p. $108-111^\circ$ at 0.03 mm; after cooling it crystallized; m.p. 32° . It is soluble in the majority of organic solvents but sparingly soluble in water.

Found %: C 59.35; H 10.41; S 12.10. $\text{C}_{13}\text{H}_{28}\text{O}_3\text{S}$. Calculated %: C 59.33; H 10.26; S 12.11.

(c) From 6.6 g (0.055 g-mole) of (III) and 5.1 g (0.05 g-mole) of cyclohexanol, was obtained, after solution in benzene, chromatography on Al_2O_3 , and evaporation of the solvent, 6.0 g (55.6%) of (XXIV) with m.p. $48-49^\circ$.

Found %: C 54.38; H 8.79; S 14.51. $\text{C}_{10}\text{H}_{20}\text{O}_3\text{S}$. Calculated %: C 54.54; H 9.12; S 14.56.

SUMMARY

1. 1-Alkylsulfinyl-2-alkoxy-, and -2-alkyl- or -aryl-, thioethanes have been obtained by the addition of alcohols and thiols to vinyl ethyl and butyl sulfoxides in the presence of "Triton B".

2. It has been shown that vinyl sulfoxides are considerably less reactive with respect to nucleophilic reagents than vinyl sulfones, and that a difference in reactivity is also observed between vinyl ethyl and butyl sulfoxides.

It has been shown on the basis of the reaction with thiols, that vinyl sulfoxides exhibit no tendency to free-radical additions.

The addition reactions to vinyl ethyl sulfone of hydrogen sulfide, ethylene glycol, propanol, nonanol, cyclohexanol, and N- β -mercaptoethylpyrrolidone have been studied and it has been shown that in the presence of "Triton B" they all add exothermically with the formation of high yields of products.

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STUDIES OF THE SYNTHESIS AND REACTIONS OF UNSATURATED ORGANO-SILICON COMPOUNDS

THE REACTION OF γ -SILICON-CONTAINING ACETYLENE CHLORIDES WITH SODIUM ACETOACETIC AND SODIUM MALONIC ESTERS

M. F. Shostakovskii, V. P. Kuznetsova and N. V. Komarov

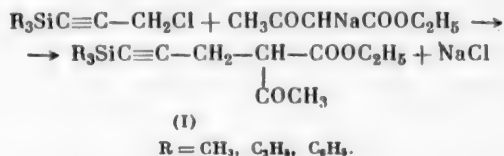
Irkutsk Institute of Organic Chemistry, Siberian Division of the Academy
of Sciences of the USSR

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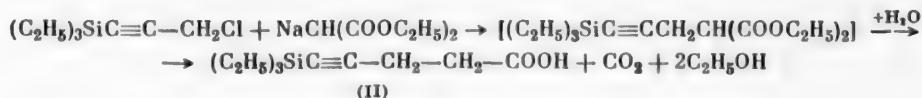
Original article submitted July 25, 1960

In previous studies [1] on the synthesis and reactions of various organo-metallic acetylenic alcohols and their derivatives, interesting data on their reactivity and synthetic possibilities were obtained. In our present work we have investigated the reaction of γ -silicon-containing acetylene chlorides of the propargyl type [2] with sodium acetoacetic and sodium malonic esters for the purpose of ascertaining the utility of these reactions for the preparation of silico-acetylenocarbonyl compounds. It was of interest to find out whether alkylation of acetoacetic and malonic esters by means of γ -silicon-containing chlorides occurs, or whether the latter are split at the Si-C bond.

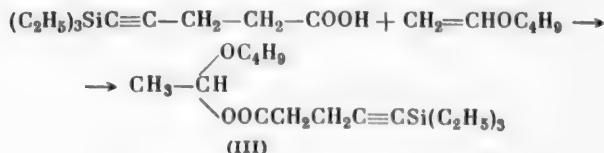
Investigation showed that primary γ -silicon-containing acetylene chlorides easily react with sodium acetoacetic ester without rupture of the Si-C bond, with the formation of the corresponding silico-acetylenic keto esters (I). The reaction goes smoothly and the yield of ketoesters reaches 40-50%.



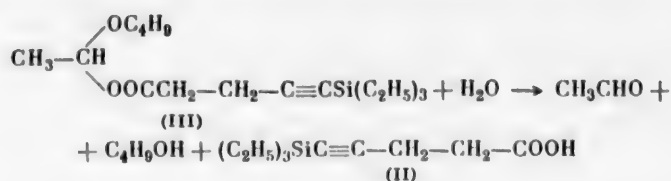
On alkylating the sodium malonic ester of 3-chloropropin-1-triethylsilane one might expect the formation of the corresponding silico-acetylenic malonic ester. However, as a result of the synthesis, silico-acetylenic acid (II) was obtained which apparently resulted from the splitting up of the silico-acetylenic malonic ester that was formed during the reaction.



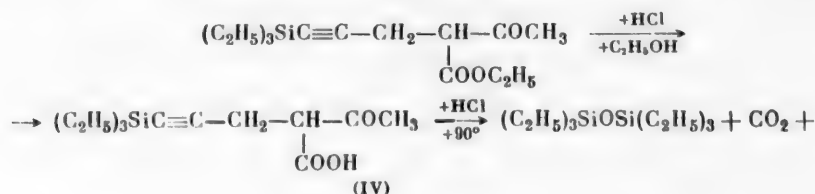
The presence of a carboxyl group in the silico-acetylenic acid was demonstrated by its reaction with vinylbutyl ester.



The reaction proceeds without a catalyst. In this way the first representative of the organo-silicon acylals (III) was obtained which contain silicon in the acid radical. Hydrolysis of the silico-acetylenic acylal proceeds as follows:



It was interesting to study the behavior of the silico-acetylenic keto esters in regard to ketonic cleavage. As an example we studied the cleavage of 6-triethylsilyl-3-carbethoxyhexyne-3-one-2. An effort to cleave this keto-ester by 10% hydrochloric acid in alcohol under mild conditions was unsuccessful, i.e., it did not result in a change in the original product. On cleaving it by the usual method (heating to 90° for 10-15 minutes) the corresponding silico-acetylenic ketoacid (IV) was obtained. Cleavage of a silico-acetylenic ketoester, carried out by the same method, but with more prolonged heating (3-4 hours at 90°), resulted in rupture of the Si-C bond and the formation of hexaethyldisiloxane as the principal product and an insignificant quantity of silico-acetylenic ketoacid. Thus, we established the fact that the cleavage of these silico-acetylenic ketoesters by an alcoholic solution of hydrochloric acid proceeds by steps, i.e., at first the silico-acetylenic ketoacid is formed which then immediately undergoes further decomposition with the rupture of the Si-C bond.



It was not possible to obtain silico-acetylenic ketone $(\text{C}_2\text{H}_5)_3\text{SiC}\equiv\text{CCH}_2\text{COCH}_3$ which would be expected on ketonic cleavage.

Condensation of tertiary γ -silicon-containing acetylene chlorides with sodium acetoacetic and sodium malonic esters did not occur.

EXPERIMENTAL

Starting materials. 3-chloropropin-1-trimethylsilane [2], b.p. 50° (17 mm), n_D^{20} 1.4546, d_4^{20} 0.9295; 3-chloropropin-1-triethylsilane [2], b.p. 72° (6 mm), n_D^{20} 1.4698, d_4^{20} 0.9262; 3-chloropropin-1-dimethylphenylsilane [2], b.p. 118° (6 mm), n_D^{20} 1.5345, d_4^{20} 1.0409; acetoacetic ester, b.p. 74° (16 mm), n_D^{20} 1.4193, d_4^{20} 1.0247; malonic ester, b.p. 195° (726 mm), n_D^{20} 1.4159, d_4^{20} 1.0553.

6-Trimethylsilyl-3-carbethoxyhexyne-5-one-2 (I) ($R = \text{CH}_3$). 0.05 g-moles of sodium ethylate, prepared from 1.15 g of metallic sodium and 20 ml of anhydrous alcohol, and 6.5 g of freshly distilled acetoacetic ester were mixed in a three-necked flask equipped with a mechanical stirrer, a dropping funnel and a thermometer. Then, with stirring and heating (50-60°), 7.35 g of 3-chloropropyne-1-trimethylsilane were added drop by drop. The mixture was heated for eight hours at 50-60° and then treated with 50 ml of water. The organic layer was separated from the aqueous layer and the latter extracted with ether. The ether layer and extracts were washed with water until they were neutral and then dried over calcined sodium sulfate. The ether was distilled off and the residue distilled in vacuo.

3.1 g (40%) of a colorless oily liquid were obtained. It was insoluble in water but easily soluble in organic solvents.

B.p. 110-111° (10mm), n_D^{20} 1.4511, n_4^{20} 0.9583, M_R^{20} 67.51; calc. 67.48. Found %: Si 11.69. $\text{C}_{12}\text{H}_{20}\text{O}_5\text{Si}$. Calculated %: Si 11.42.

6-Triethylsilyl-3-carbethoxyhexyne-5-one-2 (I) ($R = \text{C}_2\text{H}_5$). The synthesis was carried out as described above. Quantities used were: 1.84 g of metallic sodium, 30 g of anhydrous alcohol, 10.5 g of freshly distilled acetoacetic ester and 15 g of 3-chloropropyne-1-triethylsilane. 10.2 g (45%) of product were obtained.

B.p. 155-157° (10 mm), n_D^{20} 1.4585, d_4^{20} 0.9448, MR_D 81.68; calc. 81.37. Found %: Si 9.64. $C_{15}H_{26}O_3Si$. Calculated %: Si 9.95.

6-Dimethylphenylsilyl-3-carbethoxyhexyne-5-one-2 (I). [$R_3 = (CH_3)_2$ and C_6H_5]. Quantities used: 1.15 g of metallic sodium, 20 ml of anhydrous alcohol, 6.5 g of acetoacetic ester and 10.5 g of 3-chloropropyne-1-dimethylphenylsilane. 7.6 g (51%) of product were obtained.

B.p. 149-151° (6 mm), n_D^{20} 1.5095, d_4^{20} 1.0140, MR_D 89.17; calc. 87.30. Found %: Si 9.11. $C_{17}H_{22}O_3Si$. Calculated %: Si 9.29.

4-Triethylsilyl-1-carboxybutyne-3 (II). 0.69 g of metallic sodium, 15 ml of anhydrous alcohol and 4.8 g of freshly distilled malonic ester and 5.64 g of 3-chloropropyne-1-triethylsilane were used for the synthesis. 4.1 g (19%) of product were obtained.

B.p. 78-80° (10mm), n_D^{20} 1.4520, d_4^{20} 0.9478, MR_D 60.47; calc. 62.63. Found %: Si 12.86. $C_{11}H_{20}O_3Si$. Calculated %: Si 13.22.

1-Butoxyethyl ester of (4-triethylsilyl-1-carboxybutyne-3) (III). 2.8 g of 4-triethylsilyl-1-carboxybutyne-3 and 1.3 g of vinylbutyl ester were placed in a three-necked 15 ml flask equipped with a mechanical stirrer, thermometer and reflux condenser. The mixture was stirred for one hour at room temperature; during this period no evidence of reaction could be observed. Then the reaction mixture was heated for 12 hours at 70° and distilled in vacuo. 3.3 g (80%) of a product with a pleasant odor were obtained.

B.p. 94-95° (8mm), n_D^{20} 1.4572, d_4^{20} 0.9311, MR_D 91.46; calc. 92.40. Found %: Si 8.40. $C_{17}H_{32}O_3Si$. Calculated %: Si 8.79.

6-Triethylsilyl-3-carboxyhexyne-5-one-2 (IV). 5.0 g of 6-triethylsilyl-3-carbethoxyhexyne-5-one-2, 20 ml of concentrated hydrochloric acid and 20 ml of alcohol were placed in a three-necked flask equipped with a mechanical stirrer, a reflux condenser and a thermometer. The reaction mixture was heated for 10-15 minutes at 90°. After the mixture was cooled it was transferred to a separating funnel and the organic layer separated, dried over sodium sulfate and distilled in vacuo. 2.4 g (53%) of a product with a pleasant odor were obtained.

B.p. 70-72° (3 mm), n_D^{20} 1.4410, d_4^{20} 0.9408, MR_D 71.36; calc. 71.89. Found %: Si 11.05. $C_{13}H_{22}O_3Si$. Calculated %: Si 11.15.

2,4-Dinitrophenylhydrazone, m.p. 244-245°.

Cleavage of 6-triethylsilyl-3-carbethoxyhexyne-5-one-2. Quantities used: 10 ml of concentrated hydrochloric acid, 10 ml of alcohol and 3.3 g of 6-triethylsilyl-3-carbethoxyhexyne-5-one-2. The reaction mixture was heated at 90° for three hours until the evolution of carbon dioxide ceased (test with baryta water). After cooling, the organic layer was separated from the acid layer, and the latter extracted with ether. The ether layer and the extracts were combined, dried over sodium sulfate and distilled. 0.2 g of 6-triethylsilyl-3-carboxyhexyne-5-one-2 (IV) with b.p. 80-81° (10 mm) n_D^{20} 1.4410, d_4^{20} 0.9405 and 0.9 g of hexaethyldisiloxane with b.p. 94-95° (10 ml), n_D^{20} 1.4350, d_4^{20} 0.8604 were obtained.

The literature [3] shows: b.p. 231°, n_D^{20} [1.4340, d_4^{20} 0.8590].

SUMMARY

1. The reaction of primary γ -silicon-containing acetylene chlorides of the propargyl type with sodium acetoacetic and sodium malonic esters was studied. It was found that with sodium malonic ester they form silico-acetylenic acids which apparently are the cleavage products of silico-acetylenic malonic esters formed during the reaction. Rupture of the Si-C bond does not occur. In the reaction of primary γ -silico-acetylene chlorides with sodium acetoacetic ester, the corresponding silico-acetylenic keto esters are formed.

2. The reaction of γ -silico-acetylenic acids with vinyl ethers was studied and a means of preparing silico-acetylenic acylals was found.

3. The ketonic cleavage of silico-acetylenic ketoesters by an alcoholic solution of hydrochloric acid was studied. It was found that cleavage proceeds in steps; at first the silico-acetylenic ketoacids are formed, and then they decompose with the rupture of the Si-C bond.

4. The following products were prepared for the first time: 6-trimethylsilyl-3-carbethoxyhexyne-5-one-2; 6-triethylsilyl-3-carbethoxyhexyne-5-one-2; 6-dimethylphenylsilyl-3-carbethoxyhexyne-5-one-2; 6-triethylsilyl-3-carboxyhexyne-5-one-2; 4-triethylsilyl-1-carboxybutyne-3; 1-kutoxyethyl ester of (4-triethylsilyl-1-carboxybutyne-3).

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SALTS OF DIALKYLTHIOPHOSPHORIC ACIDS

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Leningrad Chemico-Pharmaceutical Institute

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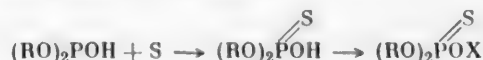
Original article submitted March 7, 1960

The salts of dialkylthiophosphoric acids have gained considerable importance as starting products for the synthesis of insecticides, fungicides, bactericides and medicinal products and also as accessory materials in the textile, paper, leather and other industries [1-3]. A study of the synthesis of these salts is of interest for clarifying the question of their structure which is still under discussion [2,4,5]. Moreover these syntheses, starting from dialkylphosphorous acids, are of value in studying the tautomerism of the latter [2,6,7].

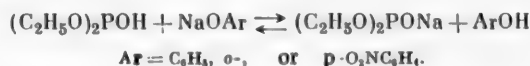
The best method of preparing the salts of dialkylthiophosphoric acids [8-11] is the addition of sulfur to the salts of dialkylphosphorous acids



(where R is alkyl) formed by the reaction of dialkylphosphorous acids with metallic sodium or potassium, which, as is well-known, is inconvenient. In this connection the addition of sulfur to dialkylphosphorous acids by heating in dioxane to 160° under pressure is important [12]. The dialkylthiophosphoric acids prepared in this way are easily converted into the corresponding salts (where X is a cation).



For the purpose of seeking a more rational method of preparing the salts of dialkylthiophosphoric acids and avoiding the use of metallic sodium or potassium, we studied the reaction of dialkylphosphorous acids with phenolates, nitrophenolates, carbonates, acetates and formates. The experiments showed that diethylphosphorous acid slowly reacts with phenolates in anhydrous alcohol with the formation of the sodium salt of diethylthiophosphoric acid.

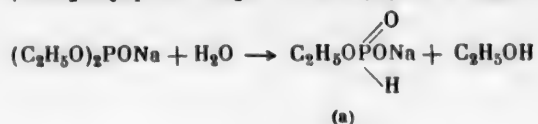


By carrying out this reaction in the presence of sulfur, the sodium salt of diethylthiophosphoric acid is rapidly and quantitatively formed.



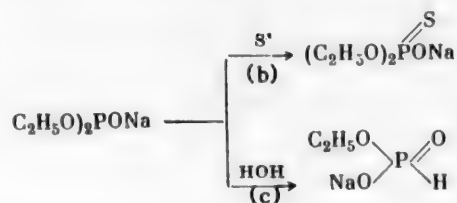
The importance of sulfur was confirmed by further experiments. Thus, on reacting diethylphosphorous acid with anhydrous sodium, potassium or ammonium carbonate or acetate under identical conditions, the formation of the corresponding salt of diethylphosphorous acid was not observed. However, when this reaction is carried out under the same conditions but in the presence of sulfur, the corresponding salt of diethylthiophosphoric acid is rapidly formed in high yield.

When diethylphosphorous acid reacts with the dihydrate of sodium p-nitrophenolate, p-nitrophenol, alcohol and the sodium salt of monoethylphosphorous acid (a) are formed quantitatively (without the addition of sulfur):



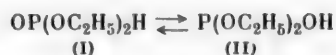
When this reaction is carried out in the presence of sulfur, p-nitrophenol is also formed quantitatively; other products of the reaction are sodium salts of diethylthiophosphoric acid (80%) and of monoethylphosphorous acid (15-20%); a part of the sulfur does not enter into the reaction.

Thus, under conditions in which the quantitative decomposition of the sodium salt of diethylphosphorous acid occurs, in the presence of sulfur the reaction proceeds preferentially in the direction of the addition of the latter, with the formation of the sodium salt of diethylthiophosphoric acid. This indicates that the rate of the addition reaction of sulfur to the sodium salt of diethylphosphorous acid (b) greatly exceeds the rate of hydrolysis of the latter (c).



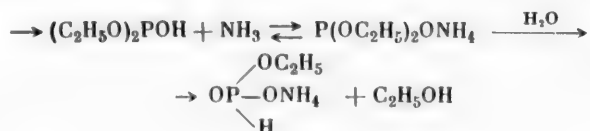
As is well-known [13], diethylphosphorous acid under the usual conditions does not react with dry ammonia or triethylamine or with sulfur; i.e., reactions that are characteristic of weak acids or compounds of trivalent phosphorus. • On the other hand when all three components react together simultaneously (diethylphosphorous acid, dry ammonia or amine and sulfur) the reaction proceeds exothermically with the quantitative formation of the corresponding salts of diethylphosphoric acid.

The comparative data presented here on the reaction of diethylphosphorous acid with phenolates, carbonates, acetates, dry ammonia or amines under identical conditions except for the presence or absence of sulfur permit the assumption that sulfur facilitates the isomerization of form (I) of diethylphosphorous acid to form (II).



In order to test the generality of this reaction, syntheses with various dialkylphosphorous acids and amines were carried out. The reaction with dry ammonia and sulfur proceeds quantitatively in dichloroethane or anhydrous alcohol. In carbon tetrachloride the yield is lower; in this case side reactions apparently occur. With amines this reaction also proceeds quantitatively; the salts formed have a neutral reaction and on standing do not give off sulfur. An exception is the reaction with phenylhydrazine; in this case oxidation of phenylhydrazine occurs along with the normal process, and part of the sulfur does not react.

The reaction with organic bases was carried out both in solvents (absolute ether, alcohol, benzene) and without them. The addition of sulfur to dialkylphosphorous acids in the presence of dry ammonia or organic bases takes place



•When dry ammonia or triethylamine reacts with an equimolecular mixture of diethylphosphorous acid and water we found that the corresponding ammonium or triethylammonium salt of monoethylphosphorous acid is formed.

more rapidly, and the formation of salts of dialkylthiophosphoric acids more energetically, than the above values of the dissociation constants of the corresponding bases. Thus, ammonia, ethyl-, diethyl- and triethylamines, and ethylenediamine react with diethylphosphorous acid in the presence of sulfur even in the cold with the formation of the corresponding salts of diethylphosphoric acid; during this reaction considerable heating is observed. When this reaction is carried out with pyridine or phenylhydrazine, moderate heating is necessary; in the case of aniline the reaction proceeds at $\sim 100^\circ$.

In order to study the influence of the nature of the cation, the reaction of diethylphosphorous acid with sulfur in the presence of the anhydrous acetates of zinc, lead, copper and calcium was investigated; the zinc salt of diethylthiophosphoric acid is formed in good yield (65%).

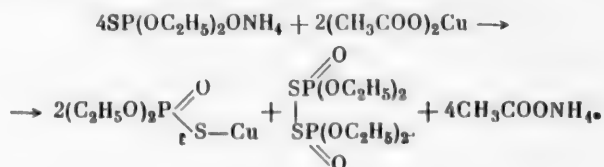


When this reaction is carried out under analogous conditions with calcium acetate, judging by analysis, the calcium salt of thiophosphoric acid $[\text{SP}(\text{OH})_2\text{O}]_2\text{Ca}$ is apparently formed.

In order to prepare the copper, lead and calcium salts of diethylthiophosphoric acid, the double exchange reactions of the ammonium (and triethylammonium) salts of diethylphosphoric acid with lead nitrate, copper acetate and calcium chloride were studied. The reaction with lead nitrate proceeds smoothly and gives lead diethylthiophosphate in 87% yield.



The reaction proceeds normally with calcium chloride, but the yield of salt is small. With copper acetate the reaction proceeds "anomalously"; instead of the diethylthiophosphate of copper (Cu^{++}), a monovalent copper salt is formed, which may be shown by the reaction



In accordance with the reaction shown, the copper salt that is formed has a thiol structure; another product of the reaction is the corresponding disulfide, obtained by the oxidation of the salt of diethylthiophosphoric acid and called "diethylthiophosphatogen" [11]. The data presented show that diethylthiophosphorous acid in these reactions is a stronger acid than acetic.

In order to study some properties of free dialkylthiophosphoric acids we prepared dimethyl- and diethylthiophosphoric acids by the action of hydrogen chloride on their ammonium salts.

EXPERIMENTAL

Experiments with nitrophenolates. 14 g of diethylphosphorous acid were gradually added, with stirring, to a homogeneous mixture of 3.2 g of sulfur, 16.1 g of sodium p-nitrophenolate and 30 ml of anhydrous alcohol; after boiling for 30 minutes the solution was evaporated to dryness. The residue was treated with ether and filtered; 19.1 g (100%) of hygroscopic crystals, m.p. $180-183^\circ$, were obtained. After recrystallization from chloroform and ether, or reprecipitation from acetone by ether the m.p. was $196-198^\circ$. A mixed melting point test with the sodium salt of diethylthiophosphoric acid, prepared according to O. Foss [11], showed no depression.

When the reaction was carried out with the dihydrate of sodium p-nitrophenolate the yield amounted to 75-78%; 20-23% of the sulfur did not react.

Experiments with acetates. 14.2 g of diethylphosphorous acid were added, with stirring, to a suspension of 8.07 g of anhydrous sodium acetate, 3.2 g of sulfur and 25 ml of anhydrous alcohol (the reaction was accompanied by the evolution of heat) and the mixture was heated to boiling for two hours. After cooling, the very small

precipitate was filtered off and washed with alcohol; 0.23 g of sulfur (5.5% of the amount used) was obtained. The filtrate was evaporated to dryness and the remainder (20.47 g) was treated with acetone and filtered (0.3 g of sodium acetate were obtained). From the acetate solution after removal of the solvent and subsequent treatment with ether, 16.75 g (88%) of hygroscopic crystals, m. p. 181-185°, were obtained.

When the reaction was conducted without a solvent the yield was 73%. The reaction proceeds in analogous fashion with sodium, potassium and ammonium acetate. The yield of the zinc salt of diethylthiophosphoric acid was 65%; it consists of glittering white crystals with m.p. 158-159° and is soluble on heating in water, alcohol and acetone, only slightly soluble in the cold, and it is not soluble in ether.

Found, %: C 23.60, 23.37; H 4.89, 5.07; S 15.34, 15.76; P 15.10 $C_8H_{20}O_6P_2Zn$. Calculated %: C 23.82; H 5.00; S 15.88; P 15.30.

Experiments with carbonates. A mixture of 6.4 g of sulfur, 21.2 g of anhydrous sodium carbonate, 29 g of diethylphosphorous acid and 100 ml of anhydrous alcohol were boiled for one hour until the sulfur was completely dissolved. After cooling and filtering, the residue was washed with alcohol (13.7 g of soda were obtained). The alcohol filtrate was evaporated to dryness, the remainder dissolved in 100 ml of acetone, the solution filtered and again evaporated to dryness; 39.5 g of hygroscopic crystals with m.p. 182-186° were obtained. The reaction with dry potassium carbonate proceeds in the same manner.

The sodium salt of monoethylphosphorous acid. A mixture of 14.5 g of diethylphosphorous acid and 19.7 g of the dihydrate of sodium p-nitrophenolate was heated for 30 minutes on a boiling water bath. The resulting transparent solution was evaporated to dryness, treated with ether and filtered. 13.5 g of material were obtained which, after recrystallization from hot alcohol, melted at 172-179°. A mixed melting point test with a known sample of sodium ethyl phosphite [14] showed no depression. p-Nitrophenol was obtained from the ether filtrate after removal of the solvent.

The sodium salt of diethylphosphorous acid. 14.5 g of diethylphosphorous acid, 16.1 g of anhydrous sodium p-nitrophenolate and 30 ml of anhydrous alcohol were boiled for 15 hours; on cooling, the precipitate was filtered off and washed with anhydrous alcohol and ether (5 g of the original sodium p-nitrophenolate were obtained). After removing the alcohol from the filtrate (in vacuo) the residue was treated with absolute ether and after a few days the yellowish needles that separated out were filtered off and washed with absolute ether. 5.3 g of extremely hygroscopic crystals were obtained which deliquesced in the air. On heating with 1.1 g of sulfur and 20 ml of alcohol, 6.1 g of the sodium salt of diethylthiophosphoric acid were obtained [11].

Experiments with ammonia and amines. The ammonium salt of diethylthiophosphoric acid. 16 g of sulfur and 300 ml of dry dichloroethane were placed in a two-necked flask joined by an adapter to a stirrer, a gas tube, a reflux condenser and a dropping funnel protected by a calcium chloride tube. Into this suspension, with energetic stirring and simultaneous passage of dry ammonia, 70.5 g of diethylphosphorous acid and 50 ml of dichloroethane were added at a rate that maintained the temperature of the reaction mixture at 75-80° (until the sulfur was completely dissolved). The crystals that separated out on cooling were filtered off, washed with dichloroethane and dried. The ammonium salts of other dialkylthiophosphoric acids were obtained in analogous fashion; all of them were easily soluble in water and insoluble in ether and dichloroethane (Table 1).

The diethylammonium salt of diethylthiophosphoric acid (II). 7.6 g of diethylamine were added to a suspension of 3.2 g of sulfur in 14 g of diethylphosphorous acid, with stirring, at such a rate that the temperature was maintained at 50-60°. When the sulfur dissolved, the reaction mass which at first had the appearance of a thick, transparent, light yellowish liquid, crystallized; after recrystallization from petroleum ether it melted at 36-42°.

The phenylammonium salt of diethylthiophosphoric acid (V). A mixture of 9.3 g of freshly distilled aniline, 3.2 g of sulfur and 14 g of diethylphosphorous acid was heated, with stirring, on a water bath until all the sulfur had reacted; 26 g of a substance were obtained which was soluble in water and organic solvents, but insoluble in petroleum ether. After reprecipitation from benzene by means of petroleum ether, or recrystallization from the latter, the m.p. was 82-83.5°. Reaction with other bases was carried out in similar fashion, while protecting the products from the moisture of the air (Table 2): with ethylamine (I), triethylamine (III), ethylenediamine (IV), dimethylaniline (VI), pyridine (VII), phenylhydrazine (IV), anabasine (IX), lupinine (X). The melting points of (VIII) and (IX) were 92-94° and 25-30° respectively; the others were oily liquids.

*The work was carried out in such a way as to protect the product from the moisture of the air.

TABLE 1. Ammonium salts of dialkylthiophosphoric acids.

Compound	M.p.	Found %		Empirical formula	Calc. %		Yield, %
		S	N		S	N	
$\text{SP}(\text{OCH}_3)_2$ **** ONH ₄	70—78°	—	—	C ₂ H ₁₈ O ₃ NSP	—	—	80 **
$\text{SP}(\text{OC}_2\text{H}_5)_2$ ONH ₄	144—145.5	16.95, 17.44	7.58, 7.50	C ₄ H ₁₄ O ₃ NSP	17.11	7.50	81 ***
$\text{SP}(\text{OC}_3\text{H}_7\text{-iso})_2$ ONH ₄	156—157	14.99, 15.20	7.19, 7.02	C ₆ H ₁₈ O ₃ NSP	15.0	6.52	80.5
$\text{SP}(\text{OC}_4\text{H}_9\text{-iso})_2$ ONH ₄	172—176	13.45, 13.46	5.44, 5.77	C ₈ H ₂₂ O ₃ NSP	13.17	5.76	91
$\text{SP}(\text{OC}_4\text{H}_9\text{-n.})_2$ ONH ₄	147—150	13.28, 13.26	5.98, 6.24	C ₈ H ₂₂ O ₃ NSP	13.17	5.76	72.5
$\text{SP}(\text{OC}_5\text{H}_{11}\text{-iso})_2$ ONH ₄	167	11.55, 11.89	5.64, 5.57	C ₁₀ H ₂₆ O ₃ NSP	11.80	5.16	92
$\text{SP}(\text{OCH}_2\text{CH}_2\text{OC}_2\text{H}_5)_2$ ONH ₄	106—110	11.14, 11.64	5.14, 5.54	C ₈ H ₂₂ O ₃ NSP	11.63	5.1	92.5
$\text{SP}(\text{OCH}_2\text{-CH=CH}_2)_2$ ***** ONH ₄	133—140	—	—	—	—	—	87.5

* If a solution of dialkylphosphorous acid in dichloroethane is added to the suspension of sulfur in dichloroethane, the yield is increased to 94 %.

** If a solution of dialkylphosphorous acid in dichloroethane is added to the suspension of sulfur in dichloroethane, the yield is increased to 96 %.

*** Found %: P 19.3, 19.4. C₂H₁₈O₃NSP, calculated %: P 19.5.

***** Found %: P 14.55, 14.7. C₆H₁₄O₃NSP, calculated %: P 14.7.

TABLE 2. Salts of diethylthiophosphoric acid and organic bases

Salt	Found, %	Empirical formula	Calc., %
(I)	14.35, 14.29	C ₆ H ₁₈ O ₃ NPS	14.38
(II)	12.40, 12.50	C ₈ H ₂₂ O ₃ NPS	12.75
(III)	11.50, 11.40	C ₁₀ H ₂₆ O ₃ NPS	11.42
(IV)	15.30, 15.20	C ₁₀ H ₃₄ O ₆ N ₂ P ₂ S ₂	15.48
(V)	11.74, 11.64	C ₁₀ H ₁₈ O ₃ NPS	11.78
(VI)	10.30, 10.45	C ₁₂ H ₂₂ O ₃ NPS	10.65
(VII)	12.00, 12.50	C ₁₀ H ₁₆ O ₃ NPS	12.42
(VIII)	11.20, 11.11	C ₁₀ H ₁₆ O ₃ N ₂ PS	11.15
(IX)	12.65, 12.83	C ₁₈ H ₃₆ O ₆ N ₂ P ₂ S ₂	12.40
(X)	9.10, 8.95	C ₁₄ H ₃₀ O ₄ NPS	9.15

The ammonium salt of monoethylphosphorous acid. Dry ammonia was passed into 27.5 g of diethylphosphorous acid in 300 ml of dry ether and 3.6 g of water until saturation occurred. After a few days standing, two layers were formed; the lower one after being separated crystallized on jarring; 14.48 g (57%) of snow-white crystals with an m.p. of 95-97° were obtained. They were soluble in water and in alcohol.

Found, %: P 24.3, 24.2. C₂H₁₀O₃NP, Calculated %: P 24.4.

The lead (a), copper (b) and calcium (c) salts of diethylthiophosphoric acid. a) a solution of 18.7 g of the ammonium salt of diethylthiophosphoric acid in 25 ml of water was added to 20 g of lead nitrate in 70 ml of water;

the thick mass that was formed quickly crystallized. After washing with water 23.7 g (87%) of a substance were obtained which, after recrystallization from hot water, melted at 45-46° and was soluble in alcohol and chloroform and slightly soluble in ether, dichloroethane, hot benzene and xylene.

Found %: C 17.63, 17.59; H 4.02, 3.75; S 11.70, 11.60. $C_8H_{20}O_6S_2P_2Pb$. Calculated %: C 17.61; H 3.67; S 11.74.
b) a solution of 30 g of the ammonium salt of diethylthiophosphoric acid in 30 ml of water was added to 65 g of copper acetate in 50 ml of water; a white precipitate was observed to form which after a few days was filtered off and washed with water. 25 g of a substance melting at 93-98° were obtained which, after treatment with acetone, melted at 102°; the latter was soluble in ether, hot alcohol, acetone, dichloroethane, benzene and xylene. Monovalent copper was detected qualitatively by a yellow precipitate with a solution of alkali, by xanthogenates (sodium, potassium) and by a white precipitate with potassium iodide.

Found %: C 20.49, 20.92; H 4.19, 4.43; S 14.23, 13.75. $C_4H_{10}O_3SPCu$. Calculated %: C 10.64, H 4.43; S 13.76.
c) 3.72 g of the ammonium salt of diethylthiophosphoric acid in 2 ml of water were added to a solution of 2.2 g of calcium chloride in 6.6 ml of water; the white precipitate formed was washed with water and dried; m. p. 136-146°.

Found %: P 15.20. $C_8H_{20}O_6S_2P_2Ca$. Calculated %: P 16.35.

The calcium salt of thiophosphoric acid. 8.3 g of calcium acetate (with 0.5 moles of water of crystallization), 14 g of diethylphosphorous acid, 3.2 g of sulfur, 20 ml of anhydrous alcohol and 20 ml of acetic anhydride were heated to boiling for nine hours; the precipitate that formed was filtered off and washed with alcohol. A crystalline mass saturated with a syrupy liquid was separated from the filtrate after removal of the solvent. After treatment with acetone it was insoluble in water and in alcohol.

Found %: P 23.40, 23.00. $CaH_4O_6S_2P_2$. Calculated %: P 23.40.

Dimethylthiophosphoric acid. Dry hydrogen chloride was passed into a suspension of 16 g of the ammonium salt of dimethylthiophosphoric acid and 50 ml of dry ether, cooled by a mixture of snow and salt, until saturation occurred. The precipitate was filtered off and washed with dry ether. After the removal of 5.1 g of ammonium chloride from the filtrate the ether was driven off in vacuo and the remainder distilled. 2.3 g of material were obtained.

B.p. 87-87.5° at 0.5 mm, n_D^{20} 1.4615, d_4^{20} 1.2480, MR_D 31.25; calc. 31.12. Found %: C 17.02, 17.08; H 4.95, 4.98; S 22.37, 22.55. $C_2H_7O_3SP$. Calculated %: C 16.90; H 4.93; S 22.53.

Diethylthiophosphoric acid was prepared by an analogous procedure; yield 65%.

B.p. 88.5-89° at 0.4 mm and 117-119° at 6 mm, n_D^{20} 1.4688, d_4^{20} 1.1643, MR_D 40.65; calc. 40.04 (for the thiol isomer 40.36).

SUMMARY

1. It was found that diethylphosphorous acid reacts with anhydrous nitrophenolates or carbonates of sodium or potassium and with sulfur with the formation of an almost quantitative yield of the sodium or potassium salts of diethylthiophosphoric acid; with the anhydrous acetates of sodium, potassium, ammonium or zinc, a yield of 90-93% of the sodium or potassium salt, 80-85% of the ammonium salt, and 65% of the zinc salt of this acid is obtained. The sodium salt of diethylthiophosphoric acid is formed with a yield of 75-80% when this reaction is carried out with the dihydrate of sodium p-nitrophenolate.

2. Diethylphosphorous acid reacts with the dihydrate of sodium p-nitrophenolate with the formation of monoethylphosphorous acid in good yield.

3. By reacting dialkylphosphorous acids with dry ammonia or organic bases and sulfur, the ammonium salts of dialkylthiophosphoric acids and salts of the corresponding bases are obtained in almost quantitative yields.

4. By reacting diethylphosphorous acid with dry ammonia in the presence of an equivalent quantity of water, the ammonium salt of monoethylphosphorous acid was obtained.

5. It was found that diethylphosphorous acid reacts with the phenolates, carbonates and acetates of sodium, potassium, ammonium or zinc as a trivalent phosphorus derivative.

6. By reacting the ammonium or triethylammonium salts of diethylthiophosphoric acid with lead nitrate, calcium

chloride or copper acetate, the corresponding diethylphosphates of lead, calcium and monovalent copper were obtained in good yield.

7. By reacting hydrogen chloride with the ammonium salts of dimethyl- and diethylthiophosphorous acid, dimethyl- and diethylthiophosphoric acids were obtained.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

II. THE PROPERTIES OF DI-(β -CHLOROETHYL)-PHOSPHOROUS ACID

V. G. Pesin and A. M. Khaletskii

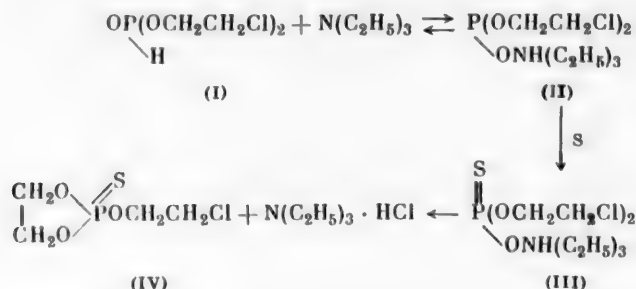
Leningrad Chemico-Pharmaceutical Institute

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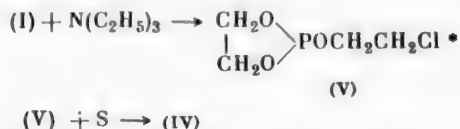
pp 2515-1518, August, 1961

Original article submitted March 10, 1960

In the preceding communication [1] convenient methods were described for the synthesis of salts of dialkylthiophosphoric acids from dialkylphosphorous acids and sulfur in the presence of nitrophenolates, carbonates, acetates (of sodium, potassium, ammonium, zinc), dry ammonia or organic bases. The present paper describes our study of the reaction of di-(β -chloroethyl)-phosphorous acid (I) with bases in the presence or absence of sulfur. In contrast to diethylphosphorous acid, the final product of the reaction (I) with dry ammonia or organic bases (diethyl- or triethylamine, piperidine) in the presence of sulfur is the β -chloroethyl ester of ethyleneglycolthiophosphoric acid (IV), and not the corresponding salt of di-(β -chloroethyl)-thiophosphoric acid (III).



The reaction shows the synthesis of compound (IV) by the addition of sulfur to the β -dichloroethylene ester of ethyleneglycolphosphorous acid (V) obtained from di (β -chloroethyl)-phosphorous acid (I) and triethylamine.

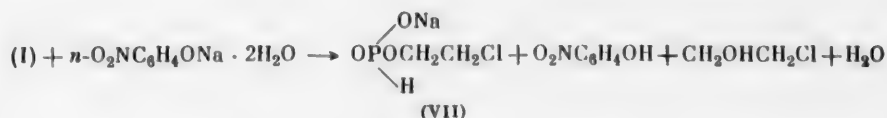


Formation of the intermediate products (salts II and III) results from the fact that the reaction of (I) with triethylamine, which gives product (V), goes extremely slowly, while the reaction of (I) with triethylamine and sulfur proceeds very energetically with quantitative formation of the ester (IV). This is in accordance with the fact that sulfur adds quickly and quantitatively to metallic derivatives of dialkylphosphorous acids with the formation of the corresponding salts of dialkylthiophosphoric acid. This scheme is also in agreement with the facts observed on carrying out the reaction under different conditions (with various bases and solvents) (see EXPERIMENTAL).

The fact that (V) is obtained by the reaction of (I) with triethylamine shows that under the experimental conditions (I) behaves as a trivalent phosphorus derivative; moreover comparison of studies of the reaction of (I)

* Compound (V) was prepared by A. E. Arbuzov [2] according to the reaction

with triethylamine in the presence and absence of sulfur makes it possible to conclude that the triethylammonium salt of di-(β -chloroethyl)-thiophosphoric acid (III) and the ester (IV) have a thione structure. In addition, this comparison strengthens the previously stated hypothesis [1] that under these conditions sulfur promotes the isomerization of form P^V dialkylphosphorous acids to form P^{III} . Analogous to diethylphosphorous acid, when di-(β -chloroethyl)-phosphorous acid (I) reacts with the dihydrate of sodium p-nitrophenolate, hydrolysis occurs with the formation of the sodium salt of mono-(2-chloroethyl)-phosphorous acid (VII); other products of the reaction are p-nitrophenol and ethylenechlorhydrin.



Di-(β -chloroethyl)-phosphorous acid was prepared by the reaction of phosphorus trichloride with ethylenechlorhydrin, with cooling, and also according to McCombie [3] (on heating to 30-35° in a solution of carbon tetrachloride).

EXPERIMENTAL

β -Chloroethyl ester of ethyleneglycolthiophosphoric acid. 10.35 g of di-(β -chloroethyl)-phosphorous acid in 10 ml of ether were added to 1.6 g of sulfur, 5.05 g of triethylamine and 40 ml of dry ether at such a rate that the boiling of the ether was maintained. When the sulfur was dissolved, two layers separated—an oily one (the salt) and ether. After 40 hours of boiling the crystalline precipitate that was formed (triethylamine chlorohydrate) was filtered off and washed with ether. The remaining material, after removal of the ether, was a transparent thick liquid which on prolonged standing was converted into an amorphous mass (the reaction was also carried out in acetone and chloroform with the use of diethylamine, piperidine or dry ammonia).

Found %: P 15.20, 15.10. $C_4H_8O_3PSCl$. Calculated %: P 15.30.

β -Chloroethyl ester of ethyleneglycolphosphoric acid. 20.7 g of di-(β -chloroethyl)-phosphorous acid, 10.3 g of triethylamine and 40 ml of xylene were heated and stirred on a boiling water bath for 13.5 hours. The white precipitate was filtered off and washed with ether (13.35 g of triethylammonium chloride were obtained). After removal of the solvent from the filtrate it was distilled at 6-6.5 mm and 7.9 g of a colorless liquid were obtained; b.p. 80-82°, d_4^{20} 1.3219, n_D^{20} 1.4758. The literature shows [2]: b.p. 78.5-79.5° at 6.5 mm, d_4^{20} 1.3206, n_D^{20} 1.4755. The reaction was also conducted in acetone and in the absence of solvent, but separation of the product in the latter case was difficult.

The reaction of the β -chloroethyl ester of ethyleneglycolphosphorous acid with sulfur. 1.6 g of sulfur were added, with stirring, to 8.55 g of the β -chloroethyl ester of ethyleneglycolphosphorous acid at 55° (heating was observed); on subsequent heating on a boiling water bath until the sulfur dissolved completely, 10 g of an almost colorless thick oily liquid were obtained.

Found %: Cl 17.35, 17.55; S 15.41, 15.67. $C_4H_8O_3PSCl$. Calculated %: Cl 17.53; S 15.80.

The sodium salt of β -chloroethylphosphorous acid. 4 g of the dihydrate of sodium p-nitrophenolate and 4.2 g of di-(β -chloroethyl)-phosphorous acid were heated for 30 minutes on a boiling water bath; after cooling, 60 ml of dry ether were added. After energetic stirring, the white crystalline precipitate that formed was filtered off, washed with ether and dried; m.p. 54-71° (apparently on increasing the temperature NaCl is split off).

Found %: P 18.70, 18.50. $C_2H_5O_3PClNa$. Calculated %: P 18.68.

From the ether filtrate ethylenechlorhydrin and p-nitrophenol were separated.

SUMMARY

1. It was found that di-(β -chloroethyl)-phosphorous acid reacts with triethylamine to form the β -chloroethyl ester of ethyleneglycolphosphorous acid, but in the presence of sulfur the β -chloroethyl ester of ethyleneglycolthiophosphoric acid is formed. The latter is also obtained by the direct addition of sulfur to the β -chloroethyl ester of ethyleneglycolphosphorous acid. These reactions show that di-(β -chloroethyl)-phosphorous acid reacts as a derivative of trivalent phosphorus and that the β -chloroethyl ester of ethyleneglycolthiophosphorous acid has a thione structure.

2. The sodium salt of mono-(2-chloroethyl)-phosphorous acid was prepared by the reaction of di-(β -chloroethyl)-phosphorous acid with the dihydrate of sodium p-nitrophenolate.

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SALTS OF DIALKYLTHIOPHOSPHORIC ACIDS

III. THE REACTIVITY AND STRUCTURE OF SALTS OF DIETHYLTHIOPHOSPHORIC ACID

V. G. Pesin and A. M. Khaletskii

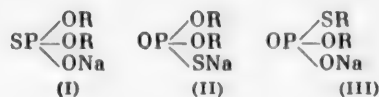
Leningrad Chemico-Pharmaceutical Institute

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Original paper submitted March 10, 1960

The structure of the salts of dialkylthiophosphoric acids may be expressed by the following formulas:



The synthesis and properties of the salts of dialkylthiophosphoric acids were carefully studied for the first time by P. S. Pishchimuka [1] who showed that their silver salts react with alkyl iodides to form esters of isothio-

phosphoric acid — $\text{OP}(\text{OR})_2$. This course of the reaction was subsequently confirmed by a number of other investi-

gators [2-6]. The esters of isothiophosphoric acid are also formed by replacing alkyl halides by dialkylsulfate [7]. On the contrary, A. E. Arbuzov and O. M. Shapshinskaya [8] found that when salts of dialkylthiophosphoric acids react with alkyl halides, esters of thione structure — $\text{SP}(\text{OR})_2$ — are formed. Acylation of the salts of diethylthiophosphoric acid leads to the formation of esters of thione structure [9].

The data given in the literature on the alkylation and acylation of the salts of dialkylthiophosphoric acids referring to their double reactivity, makes it necessary to raise the question of their structure. P. S. Pishchimuka [1] attributed this to their thiol structure; V. Mastin and co-workers assumed that the potassium salt of diethylthiophosphoric acid is an equilibrium mixture of isomers (no proof was offered). G. Shrader assumes the tautomerism: (I) \rightleftharpoons (II). A. E. Arbuzov [8], M. I. Kabachnik [6], and R. Gore [11] suggest that alkaline salts of dialkylthiophosphoric acids have a thione structure. G. Kosolapov [12] thinks that they have a thiol structure. N. N. Mel'nikov and co-workers [13] point out that the sodium salt of diethylthiophosphoric acid reacts with aryl diazonium salts in two tautomeric forms (I and II).

Thus, a survey of the literature shows that at the present time there is no unified opinion on the structure of the salts of dialkylthiophosphoric acids.

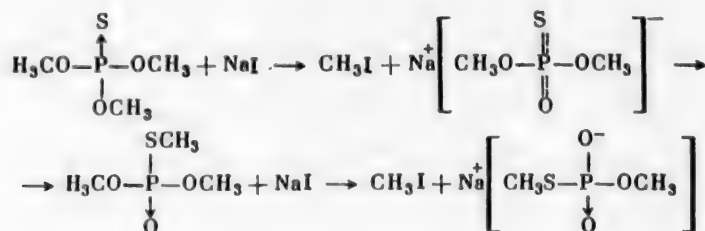
A study of the synthesis of these salts, and also of the properties of dialkylphosphoric acids [14] permitted us to come to a conclusion concerning the thione structure of the salts (I). Insofar as structure (III), which was mentioned above, is concerned, it was first reported on in the paper of W. Emmet and H. Jones [2] who showed that the sodium salt of dimethylthiophosphorous acid, prepared by the reaction of sodium methylate with thione ester $\text{SP}(\text{OCH}_3)_2$ has structure (I), while the salt prepared from sodium methylate and thiolester — $\text{OP}(\text{OCH}_3)_2\text{SCH}_3$ — has structure (III). The authors drew this conclusion on the basis of the fact that the latter, i.e., (III), behaves like a thiol ester in relation to silver nitrate.

G. Hilgetag and H. Teichmann [15] recently showed that when sodium methylate reacts with trimethylthio-

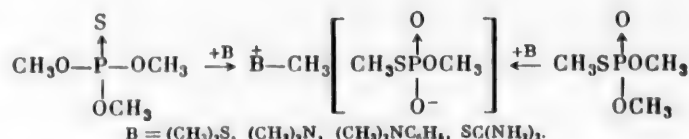
* M. I. Kabachnik [6], referring to the constants obtained for the esters by A. E. Arbuzov, suggested that the thiol isomer was formed in the latter's experiments also.

phosphate there is formed, not $\text{OP}(\text{OCH}_3)\text{SCH}_3$, but a mixture of substances with a low sulfur content. The pure

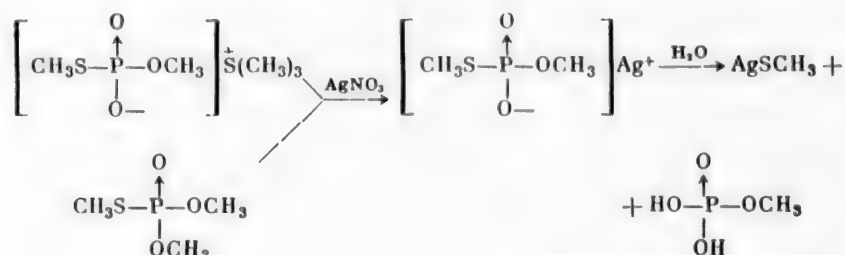
product (III) was prepared by the reaction of trimethylthione- or trimethylthiolphosphate with sodium iodide at 40-45° in acetone.



Salt (III) was also prepared by the reaction of trimethylthione- or trimethylthiolphosphate with bases (trimethylamine, dimethylaniline, pyridine), with dimethylsulfide, and also with thiourea [15].

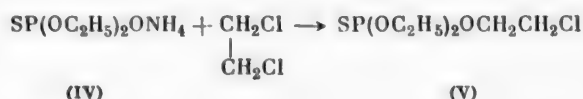


Salt (III) differs from salts (I or II) in its relation to silver nitrate; in this case silver mercaptide is formed which is the decomposition product of an extremely unstable silver salt of O,S-dimethylthiophosphoric acid. The same thing occurs when trimethylthiolphosphate reacts with silver nitrate, as mentioned by Emmet and Jones [2].

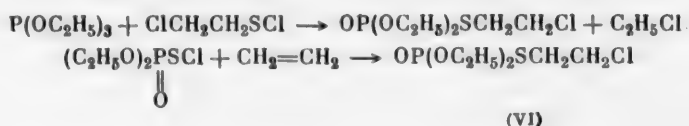


It was not possible to separate free O,S-dimethylthiophosphoric acid by acidifying its salts with mineral acids; the free acid was obtained by passing an aqueous solution of the salt through a column of "Vofatit KPS 200" and subsequently concentrating in vacuo.

The data presented in the present paper on our study of the reaction of sodium, ammonium and triethylammonium salts of diethylthiophosphoric acid with ethyl chloride and ethyl iodide and also with dichloroethane show that a thiol or thione ester is formed in these reactions depending on the nature of the alkyl halide. Thus, for example, when these salts react with ethyl iodide or chloride, the triethyl ester of isothiophosphoric acid $\text{OP}(\text{OC}_2\text{H}_5)_2\text{SC}_2\text{H}_5$ is formed. On the other hand, the reaction of the ammonium salt of diethylthiophosphoric acid (IV) with dichloroethane gives an ester with a thione structure (V).

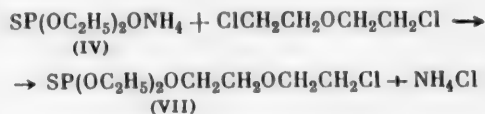


Structure (V) follows from comparison of its properties with the properties of the isomeric diethyl-S-2-chloro-ethylthiophosphate (VI) prepared by the following reaction [16-18].



(VI)

An ester of thione structure (VII) is apparently also formed by the reaction we carried out between the ammonium salt of diethylthiophosphoric acid and β , β -dichlorodiethyl ether.



The formation of esters of thione form from the ammonium salt of diethylthiophosphoric acid and alkyl halides is a supplementary proof of the thione structure of the salt, inasmuch as the isomerization of the thiol esters to the thione esters is unknown. The reaction which we studied between the ammonium salts of diethylthiophosphoric acid and phosphorus pentachloride points toward the thione structure of these salts; in this case the chloride of diethylthiophosphoric acid was obtained in 80% yield.



This reaction, apart from its theoretical interest, is of practical importance as a convenient method of preparing the chloride of diethylthiophosphoric acid.

EXPERIMENTAL

The triethyl ester of isothiophosphoric acid. 28 g of diethylphosphorous acid in 25 ml of absolute ether were added, with stirring, to 6.4 g of sulfur, 20.2 g of triethylamine and 75 ml of absolute ether at such a rate that the ether was just maintained at the boiling point. After all the sulfur had gone into solution, the reaction mixture was heated for 15 minutes to boiling and then cooled. 32 g of ethyl iodide were added to the transparent yellow solution. Then the mixture was boiled for four hours, cooled and the precipitate filtered off and washed with ether; 45.3 g of triethylammonium iodide were obtained. The ether was removed from the filtrate in vacuo and the remaining material distilled; 35.6 g (90%) of a colorless liquid were obtained; b.p. 95-96° at 2 mm, n_D^{20} 1.4570 (the literature shows n_D^{20} 1.4570 [19]).

When the reaction with the ammonium salt of diethylthiophosphoric acid was carried out in boiling anhydrous alcohol the yield was 64.5%; on heating this salt with ethyl chloride in acetone in an autoclave on a boiling water bath the yield was 59%; on heating the sodium salt of diethylthiophosphoric acid with ethyl iodide and anhydrous alcohol the yield was 40%. The thiol ester was obtained in all cases.

The β -chloroethyl ester of diethylthiophosphoric acid. 37.4 g of the ammonium salt of diethylthiophosphoric acid, 150 ml of dichloroethane and 30 ml of alcohol were heated to boiling for 25 hours; the precipitate was then filtered off and washed with alcohol. After removal of the alcohol and dichloroethane from the filtrate, the remaining material was distilled. The following fractions were obtained: 100-107° at 4.5 mm, n_D^{20} 1.4640, 107-121° at 4-5 mm, n_D^{20} 1.4652. For the thiol isomer the literature shows 147° at 5 mm n_D^{20} 1.2036, n_D^{20} 1.4750. Both samples were colorless liquids, and judging by the analytical results, were fairly pure.

Found %: P 13.30, 13.25. $\text{C}_7\text{H}_{14}\text{O}_3\text{PSCl}$. Calculated %: P 13.31.

The chloride of diethylthiophosphoric acid. 42.5 g of phosphorus pentachloride were dissolved by heating in 125 ml of carbon tetrachloride and, after cooling, 37.4 g of the ammonium salt of diethylthiophosphoric acid were added, with stirring (evolution of heat occurred). Then the reaction mixture was heated to boiling for one hour and

the precipitate filtered off and washed with CCl_4 (10.35 g of ammonium chloride were obtained). After distilling the carbon tetrachloride and the phosphorus oxychloride from the filtrate, the remaining material was distilled and 30.1 g (80%) of a colorless liquid were obtained; b.p. 90-91° at 12-14 mm, n_D^{20} 1.4693 (the literature shows n_D^{20} 1.4685 [20]).

SUMMARY

1. It was found that the sodium, ammonium and triethylammonium salts of diethylthiophosphoric acid react with ethyl iodide or chloride to form the triethyl ester of isothiophosphoric acid.

2. It was shown that the ammonium salt of diethylthiophosphoric acid reacts with dichloroethane to form an ester of thione structure — β -chloroethyldiethylthiophosphate.

3. It was found that the ammonium salt of diethylthiophosphoric acid reacts with phosphorus pentachloride and forms the chloride of diethylthiophosphoric acid in high yield.

4. The experimental data relating to the synthesis and properties of the salts of dialkylthiophosphoric acids leads to the conclusion that the latter have a thione structure.

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SALTS OF DIALKYLTHIOPHOSPHORIC ACIDS

IV. REACTIONS OF SALTS OF DIALKYLTHIOPHOSPHORIC ACIDS WITH AROMATIC AND HETEROCYCLIC HALOGEN DERIVATIVES

V. G. Pesin, A. M. Khaletskii and I. G. Vitenberg

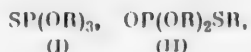
Leningrad Chemico-Pharmaceutical Institute

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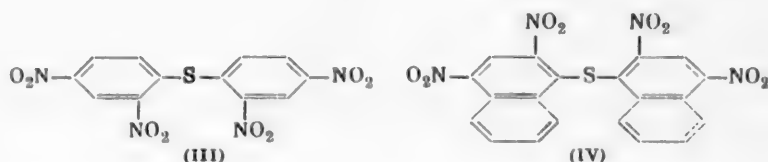
It is well known that alkaline salts of dialkylthiophosphoric acids can react in two ways. For instance, when they react with halogen derivatives of the aliphatic series they form two series of derivatives: esters of thione (I) or of thiol (II) structure.



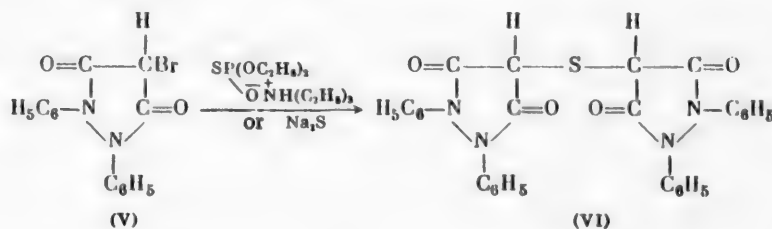
R - alkyl, aralkyl or acyl

In a preceding study [1] it was shown that the character of the alkyl halide has an influence on the direction of the reaction when the salts of dialkylthiophosphoric acids react with aromatic halogen derivatives, but there is no data of this sort in the literature except for one mention of the fact that sodium chloride was not found on heating the sodium salt of diethylthiophosphoric acid with *n*-nitrochlorobenzene to 120° [2].

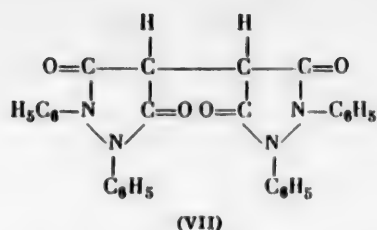
In order to investigate the mechanism of this reaction we undertook a study of the relation of dialkylthiophosphoric acids to aromatic and heterocyclic halogen derivatives. The experimental data showed that the direction of the reaction depends on the nature of the radical of the halogen derivative. Thus, 2,4-dinitrochlorobenzene reacts with the sodium, potassium, ammonium or triethylammonium salt of diethylthiophosphoric acid [3] to form 2,4,2',4'-tetranitrobiphenylsulfide (III) [4]; the reaction with 2,4-dinitrochloronaphthalene (IV) [5] proceeds in similar fashion.



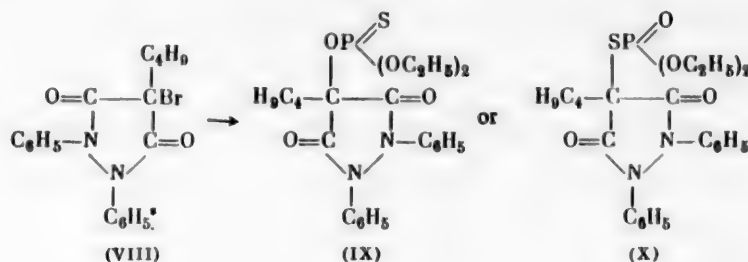
When this reaction is carried out with heterocyclic halogen derivatives it proceeds for the most part in two directions. Thus, 4-bromo-1,2-diphenyl-3,5-dioxypyrazolidine (V) reacts with triethylammonium diethylphosphate analogously to the reaction of the latter with 2,4-dinitrochlorobenzene to form the sulfide (VI), the structure of which was proved by synthesis according to the reaction:



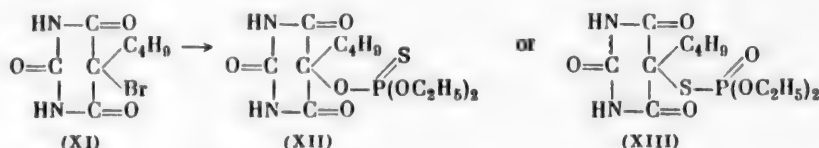
Bis (1,2-diphenyl-3,5-dioxypyrazolidine) (VII) was obtained as a byproduct.



When this reaction was carried out with 4-bromo-4-n-butyl-1,2-diphenyl-3,5-dioxypyrazolidine (VIII) an ester of thione structure (IX) or thiol structure (X) [6] was obtained, but not the sulfide as in the case of the reaction of (V) with $SP(OC_2H_5)_2OX^+$, where $X = Na, K, NH_4, NH(C_2H_5)_3$.

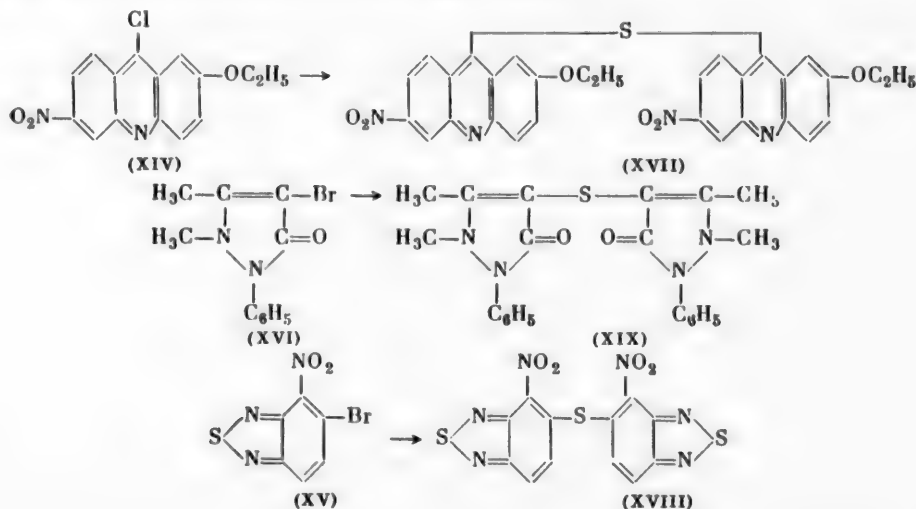


5-Bromo-5-n-butylbarbituric acid (XI) undergoes this reaction analogously to (VIII), i.e., an ester of thione (XII) or thiol (XIII) structure is also formed.



On the other hand, 2-ethoxy-6-nitro-9-chloroacridine (XIV), 4-nitro-5-bromobenz-2,1,3-thiadiazol (XV) and 4-bromoantipyrin (XVI) react with an ammonium or triethylammonium salt of diethylthiophosphorous acid to give the corresponding sulfides (XVII, XVIII, XIX).

In order to study the influence of halogen on this reaction, it was also carried out with 2,4-dinitrofluorobenzene; the experimental data show that the process proceeds with great rapidity.



Name of halogen derivative	Reaction product	Solvent for re-crystallization	Yield, %	M.P.	Found, %		Empirical formula	Calc. %	
					N	S		N	S
2,4-Dinitrochloro- or fluorobenzene	2,4,2',4'-tetranitrodi-phenylsulfide (III) [4]	Nitrobenzene	85.60	192—193° [4]	15.24, 15.57	8.65, 8.77	$C_{12}H_6O_8N_4S$	15.30	8.74
2,4-Dinitrochloro-naphthalene [5]	2,4,2',4'-tetranitrodi-naphthylsulfide (IV) [7]	Same	97.00	269—270 [7]	11.84, 11.93	7.02, 7.06	$C_{20}H_{10}O_8N_4S$	12.0	6.87
4-Bromoantipyrin [3]	Di(1-N-phenyl-2,3-di-methyl-5-pyrazolonyl)-sulfide-4 (XIX)	Benzene	60.50	245 [9]	13.75, 14.05	7.30, 7.20	$C_{22}H_{22}O_2N_4S$	13.79	7.88
2-Ethoxy-6-nitro-9-chloroacridine	Di(2-ethoxy-6-nitroacri-dyl)-sulfide-9 (XVII)	Nitrobenzene	96.30	272—273	9.74, 9.59	5.57, 5.20	$C_{30}H_{22}O_6N_4S$	9.89	5.65
5-Bromo-5-n-butyl-barbituric acid [10-11]	5-n-Butyl-5-diethylthio-phosphorylbarbituric acid (XII or XIII)	50% alcohol	22.00	152—153	8.13, 8.17	8.80, 9.01	$C_{12}H_{21}O_6N^2S^1$	7.95	9.09
4-Nitro-5-bromo-benz-2,1,3-thio-diazol [12]	Di(4-nitrobenz-2,1,3-thio-diazolyl)-sulfide-5 (XVIII)	Precipitation from benzene by petroleum ether	85.30	156	21.40, 21.07	21.42	$C_{12}H_4O_4N_8S_2$	24.59	24.48

EXPERIMENTAL

2,4,2', 4'-Tetranitrodiphenylsulfide. 2.71 g of the triethylammonium salt of diethylphosphoric acid (prepared from 1.38 g of diethylphosphorous acid), 0.32 g of sulfur 1 g of triethylamine, 2.02 g of 2,4-dinitrochlorobenzene and 25 ml of alcohol were boiled, with stirring, for five hours. The precipitate was filtered off and washed with alcohol and water; 1.57 g of a substance with a m.p. of 192-193° were obtained (recrystallization from nitrobenzene did not change the melting point). Similar data were obtained on carrying out this reaction with the sodium and ammonium salts of diethylthiophosphoric acid [3]. Reactions with other halogen derivatives are shown in the table.

SUMMARY

1. It was found that halogen derivatives of the aromatic series react with salts of diethylthiophosphoric acids to form the corresponding sulfides with an Ar-S-Ar structure.
2. It was found that heterocyclic halogen derivatives react with salts of diethylthiophosphoric acid to form the corresponding sulfides with an R-S-R structure, or esters of thio-SP(OR)₃ or isothiophosphoric acid OP(OR)₂SR. The anomalous course of the reaction to form products of R-R composition was also noted.
3. A convenient new method for synthesizing some sulfides of the aromatic and heterocyclic series was found.

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SYNTHESIS AND REACTIONS OF GLYCOLS OF THE δ - SERIES

I. A STUDY OF THE REACTIONS OF 2,3,6-TRIMETHYL-5-KETOHEPTENE -3-DIOL-2,6

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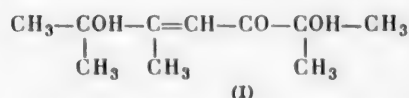
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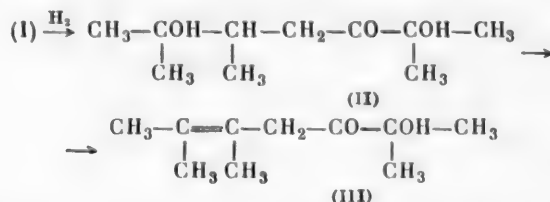
It is well-known that δ -glycols readily dehydrate thus forming substituted tetrahydropyrans. Carbonyl and hydroxyl derivatives of these heterocyclic compounds have been very little studied, as well as the mechanism of their formation.

I. N. Nazarov [1] showed that dimethylacetylcarbinol, when heated in a weak alkaline solution, condenses to form an unsaturated δ -ketoglycol - 2,3,6-trimethyl-5-ketoheptene-3-diol-2,6 (I) but he did not prove the structure.



We synthesized this glycol and in order to prove its structure, we oxidized it, ozonized it, and hydrogenated it over Pt black. By the addition of one molecule of hydrogen to glycol (I) we expected to obtain a saturated ketoglycol and study its reaction with sulfuric acid, as well as to carry out this reaction with glycol (I).

However the hydrogenation of glycol (I) gave unexpected results. After the addition of one mole of hydrogen and the removal of alcohol, the remaining material was distilled *in vacuo*. The product obtained was not a ketoglycol, but the unsaturated ketoalcohol 2,3,6-trimethyl-5-ketoheptene-2-ol-6 (III) with a double bond in the 2,3 position, which was the dehydration product of the originally formed ketoglycol - 2,3,6-trimethyl-5-ketoheptane-diol-2,6 (II).

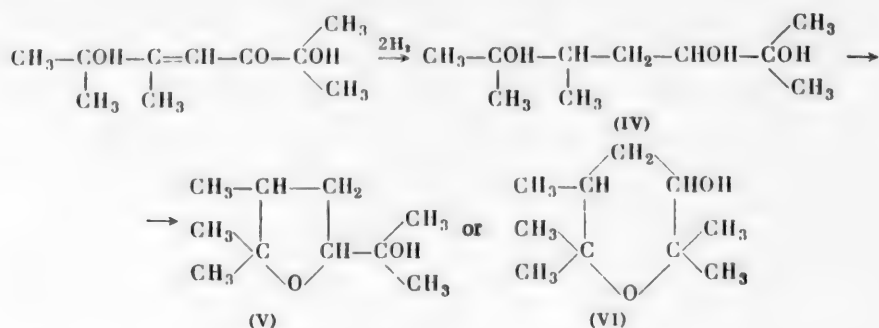


Ketoglycol (II) may be obtained if the alcohol is not distilled off, but allowed to evaporate in the cold, but in this case the yield of ketoglycol is very small, since most of it evaporates with the alcohol.

The more easily the dehydration of ketoglycol (II) occurs, the more easily the hydration of ketoalcohol (III) takes place. When compound (III) stands in a closed vessel, a small quantity of crystals of the saturated ketoglycol (II) is formed. The structure of ketoalcohol (III) was established by oxidizing it with a solution of potassium permanganate and by means of the infrared spectrum. As a result of the oxidation, acetone, hydroxyisobutyric acid and the saturated ketoglycol (II) were obtained. The formation of the latter may be explained by the fact that under the influence of the KMnO_4 solution, hydration of a double bond occurs; such examples are well-known in the literature [2]. Further oxidation and cleavage of ketoglycol (II) by the potassium permanganate solution does not occur under the reaction conditions. One might suppose that ketoalcohol (III) contains a certain quantity of dehydrated ketoglycol dissolved in it; however, analyses for the elements in the liquid up to the point where the crystals precipitated, and after they had been filtered off, proved to be identical and corresponded with the theoretical. The

the presence of a double bond in ketoalcohol (III) was proved by hydrogenation which required the amount of hydrogen calculated for one double bond.

The addition of one molecule of hydrogen to ketoglycol (I) occurs very rapidly, but hydrogenation does not stop at this point. If hydrogen continues to be passed through, the addition of one more molecule of hydrogen at the double bond of the carbonyl groups slowly takes place. It was not possible to separate out the glycerin - 2,3,6-trimethylheptanetriol-2,5,6 (IV) formed by this treatment; if the hydrogenation is carried out in alcohol and the latter is evaporated in the cold then all the hydrogenation product evaporates with the alcohol. When hydrogenation is carried out in tetrahydrofuran, absorption of only one molecule of hydrogen occurs. When the alcohol is removed by heating, dehydration of the glycerine occurs with the separation of water at the expense of two hydroxyl groups and the formation of a heterocyclic compound of the furan or pyran series.



The analytical data, molecular refraction, the presence of one hydroxyl, and the absence of a double bond and a carbonyl group, which were confirmed by chemical and spectroscopic methods, all indicated the cyclic nature of the product obtained. The compound does not hydrogenate, but slowly decolorizes a solution of potassium permanganate. It was oxidized, but the oxidation products: acetone, CO_2 , the saturated ketoglycol (II) and a negligible quantity of acid which, on the basis of the neutralization equivalent and its ability to decolorize a solution of KMnO_4

might be assigned the formula 3,4-dimethylpentene-3-acid $\text{CH}_3-\text{C}(\text{CH}_3)=\text{C}-\text{CH}_2-\text{COOH}$, did not make it possible

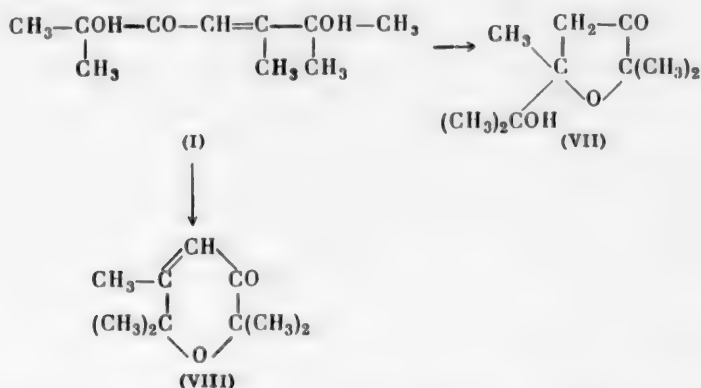
to choose between formulas (V) and (VI). Nevertheless we consider it probable that formula (VI) is correct. In glycerin (IV) the separation of water might more readily occur at the expense of two tertiary hydroxyl groups than at the expense of a tertiary and a secondary group. Moreover, on heating compound (V) with dilute sulfuric acid, which we did, it should be easily dehydrated, while the product we obtained, which contained a secondary hydroxyl group, came through the reaction unchanged. Likewise it remained unchanged on treatment with sodium in liquid ammonia. Derivatives of tetrahydrofuran under these conditions are converted into saturated alcohols with an open carbon chain. On the basis of these considerations we have assigned the formula 2,2,5,6,6-pentamethyl-4-oxytetrahydropyran (VI) to the cyclic compound we obtained.

It is known that γ -glycols, on steam distillation from a weak acid solution (pH 1.6) are converted into β -ethylene alcohols, or into substituted tetrahydrofurans, or into a mixture of both of these compounds [3]. On distilling the unsaturated ketoglycol (I) under these conditions, it was recovered completely unchanged. On boiling with 5% sulfuric acid the glycol was converted into tar; the same thing happened when the glycol was distilled in vacuo over pumice which was wet with concentrated sulfuric acid.

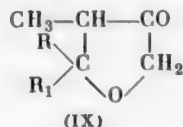
When glycol (I) was treated with concentrated sulfuric acid at -10 to -15° we succeeded in obtaining about 50% of a crystalline substance with a m.p. of $121-122^\circ$. However at this temperature the substance does not melt completely; a very small residue melts considerably higher - at $158-160^\circ$. Despite repeated experiments it was not possible to separate the mixture by recrystallization. The product did not decolorize a solution of potassium permanganate, did not hydrogenate over Pt black and did not give derivatives at the carbonyl group. It was only possible to observe the latter spectroscopically.

On reacting the unsaturated ketoglycol (I) with sulfuric acid, one might expect its isomerization into substituted tetrahydrofuranone - 2,2,5-trimethyl-5(β -hydroxyisopropyl) tetrahydrofuranone-3 (VII), or the separation

of water from two hydroxyl groups with the formation of substituted dihydropyranone - 2,2,5,6,6-pentamethyl-3-ketodihydropyran-3 (VIII).

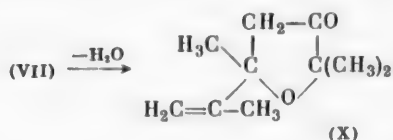


Repeated analyses showed a somewhat higher content of carbon and a somewhat lower quantity of active hydrogen atoms than would be required for tetrahydrofuranone (VII).



Tetrahydrofuranones of type (IX) easily decompose, on heating with alkali, to the ketone and acetic acid [4]. But unlike them this product did not decompose on heating with a 75% solution of caustic potash, did not reduce when treated with sodium in liquid ammonia, did not benzoylate by the Schotten-Baumann reaction and did not give derivatives on the carbonyl group.

On heating with 10% sulfuric acid, part of the substance was recovered unchanged and part dehydrogenated. The product obtained decolorized a solution of potassium permanganate, did not react with magnesium methyl iodide, and gave a characteristic precipitate with 2,4-dinitrophenylhydrazine. The analytical data and the molecular refraction correspond well with the structure 2,2,5-trimethyl-5-isopropenyl-3-ketotetrahydrofuran (X).



It was impossible to study this compound further because of the small quantity available; however, the fact that this product was obtained points to the fact that it may only be formed as a result of the dehydration of tetrahydrofuranone (VII) and strengthens our opinion that when ketoglycol (I) reacts with concentrated sulfuric acid the basic product is (VII) with a very small admixture of dihydropyranone (VIII).

It is interesting to note that the ketoglycols, ketoalcohol and tetrahydrofuranone (VII) which contain hydroxyl groups alongside a carbonyl group or at some distance from it, do not form derivatives that are characteristic of carbonyl-containing compounds; the carbonyl group in them can only be detected by spectroscopy. On the other hand, tetrahydrofuranone (X) - the dehydration product of (VII) - easily forms 2,4-dinitrophenylhydrazone.

In the infrared spectra of the hydroxyl derivatives enumerated frequencies were observed that are characteristic of hydroxyl groups joined by an intramolecular or intermolecular hydrogen bond.

EXPERIMENTAL

Synthesis of 2,3,6-trimethyl-5-ketoheptene-3-diol-2,6 (I). The ketoglycol was prepared according to the method of I. N. Nazarov [1] by the condensation of dimethylacetylcarbinol in the presence of caustic potash. A solution of 0.6 g of KOH in 6 ml of methyl alcohol was added to 78 g of dimethylacetylcarbinol. The water and methyl alcohol were distilled from this mixture at atmospheric pressure and then the remainder was distilled in vacuo; it consisted of unreacted dimethylacetylcarbinol and the ketoglycol which crystallized in the receivers. The unreacted dimethylacetylcarbinol was again subjected to the same treatment. The yield of glycol after three treatments was 37 g (52%).

I. N. Nazarov recommends distilling off the dimethylacetylcarbinol at atmospheric pressure; however, the necessity, under these conditions, of prolonged heating above 100° reduces the yield of ketoglycol and the product is less pure. On standing, as Nazarov also noted, it turns yellow and deliquesces. The pure ketoglycol can be kept for a long time without change.

B.p. 121-122° (15 mm), m.p. 82°. The literature shows [1]: b.p. 120-121° (16), m.p. 82°.

The ketoglycol does not form derivatives at the carbonyl group.

Ozonization of 2,3,6-trimethyl-5-ketoheptene-3-diol-2,6. Since on oxidation of this glycol no products other than acetone, acetic acid and CO₂ could be obtained, 3.45 g of glycol were ozonized. The ozonide was decomposed with water and the solution neutralized with soda; the neutral products were distilled into a solution of 2,4-dinitrophenylhydrazine. The resulting precipitate had a m.p. of 122-123° and showed no depression in a mixed melting point test with the 2,4-dinitrophenylhydrazone from a known sample of acetone. The remaining neutral solution was placed in an extractor, the extract dried over MgSO₄, the ether distilled off and the remaining material distilled at 141-143° at atmospheric pressure. The 2,4-dinitrophenylhydrazone had a m.p. of 145-146° and showed no depression in a mixed melting point test with a known sample of dimethylacetylcarbinol.

The acid products were extracted with ether. After drying over MgSO₄ and evaporation of the ether, the acid was separated out in the form of long needles. Purification by means of sublimation gave a m.p. of 79-80°. Hydroxyisobutyric acid has a m.p. of 79°.

Found: neutr. equiv. 105.8, 100.0. Calculated: 104.

For confirmation of the structure of the unsaturated ketoglycol (I) its infrared spectrum was taken in the region from 2900 to 3800 cm⁻¹ with a LiF prism and from 1560 to 1900 cm⁻¹ with a NaCl prism. The following frequencies

were found: 3031 cm⁻¹ (C-H in compounds of type $\begin{array}{c} R_1 \quad R_3 \\ \diagdown \quad \diagup \\ C=C \\ \diagup \quad \diagdown \\ R_2 \quad H \end{array}$), 3374 and 3428 cm⁻¹ (OH groups joined by a

hydrogen bond), 3612 cm⁻¹ (free OH group), 1604 cm⁻¹ ($\begin{array}{c} \diagup \quad \diagdown \\ C=C \\ \diagdown \quad \diagup \end{array}$ group, joined with carbonyl), 1684 cm⁻¹

(carbonyl group linked with a double bond).

Hydrogenation of 2,3,6-trimethyl-5-ketoheptene-3-diol-2,6 (I) by one volume of hydrogen. 5 g of ketoglycol were hydrogenated in 40 ml of alcohol over 0.5 g of Pt black. The hydrogenation was very rapid and was stopped after the absorption of the amount of hydrogen calculated for the hydrogenation of one double bond. The alcohol was distilled off and the remaining material distilled twice in vacuo. B.p. 76° 910 mm, yield 2.2 g (44%). The substance rapidly turned yellow, and crystallization occurred on standing. Analysis of the material before crystallization, and after the crystals had been filtered off, gave the same results. The liquid product was the unsaturated alcohol (III).

B.p. 76° (10mm), n_D^{20} 1.4518, d_4^{20} 0.9416, MR_D 48.66. C₁₀H₁₈O₂ F. Calculated 49.45. Found %: C 69.91, 70.07; H 10.46, 10.79. H_{act}. number 1.12, 1.07. M 164, 173. C₁₀H₁₈O₂ F. Calculated %: C 70.58; H 10.58. H_{act}. number 1, M 170.

The ketoalcohol (III) does not give precipitates with 2,4-dinitrophenylhydrazine and semicarbazide.

Oxidation of the unsaturated ketoalcohol (III). 14.3 g of potassium permanganate were required to oxidize 5.2 g of the compound. Among the neutral oxidation products acetone was detected by means of the 2,4-dinitrophenylhydrazones, m.p. 120-121° (mixed point). The saturated ketoglycol (II) - 2,3,6-trimethyl-5-ketoheptanediol-2, 6, b.p. 89-90° - was also detected among the neutral products. It did not decolorize a permanganate solution and did not give precipitates with 2,4-dinitrophenylhydrazine and semicarbazide.

Found %: C 64.29, 63.94; H 10.73, 10.63. H_{act} , number 2.05, 2.37. $C_{10}H_{20}O_3$. Calculated %: C 63.83; H 10.63. H_{act} , number 2.

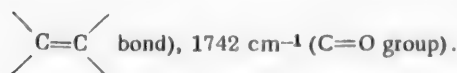
On acidifying a solution of the salts a large quantity of carbon dioxide was given off. Hydroxyisobutyric acid was separated by extracting the acid solution in an extractor. After sublimation the m.p. was 78-79° (mixed m.p.).

In order to avoid the dehydration of the saturated ketoglycol formed by the addition of a molecule of hydrogen to the unsaturated ketoglycol (I), the alcohol solution obtained from the hydrogenation of 2.5 g of ketoglycol (I) was poured into a crystallizing dish and the alcohol evaporated in the cold. After evaporation of the alcohol there remained about 0.1 g of crystalline ketoglycol with a m.p. of 88-89°. A mixed melting point test with the previously prepared saturated glycol - 2,3,6-trimethyl-5-ketoheptane-diol-2,6 - showed no depression. The crystals that precipitated on standing from the unsaturated ketoalcohol (III) also had a m.p. of 89-90° and showed no depression of the melting point in a test with a known sample of the saturated ketoglycol.

Hydrogenation of 2,3,6-trimethyl-5-ketoheptene-2-ol-6 (III). The unsaturated ketoalcohol (III) obtained on hydrogenation of the unsaturated ketoglycol (I) was again hydrogenated. 1 g of it was hydrogenated in an alcohol solution over 0.1 g of Pt black during which it absorbed the quantity of hydrogen calculated for one double bond; the hydrogenation was very slow. The alcohol was distilled off and the remaining material was distilled in vacuo.

B.p. 84° (21 mm), n_D^{20} 1.4432, d_4^{20} 0.9223, MR_D 49.91; calc. 49.92. Found %: C 69.94, 70.08; H 11.50, 11.60. H_{act} , number 1.05. $C_{10}H_{20}O_2$. Calculated % C 69.77; H 11.63. H_{act} , number 1.

In order to establish the structure of 2,3,6-trimethyl-5-ketoheptene-2-ol-6 (III) its infrared spectrum was taken in the 1560-1900 cm^{-1} region with an NaCl prism. The following frequencies were found: 1668 cm^{-1} (unlinked



The infrared spectrum of 2,3,6-trimethyl-5-ketoheptanediol-2,6 (II) was taken with a LiF prism in the 2900-3800 cm^{-1} region and with an NaCl prism in the 1560-1900 cm^{-1} region. The following frequencies were found: 3050 cm^{-1} (OH group linked by a strong intramolecular bond), 3428 cm^{-1} (OH group linked by a hydrogen bond), 1684 and 1742 cm^{-1} (C=O group).

Hydrogenation of 2,3,6-trimethyl-5-ketoheptene-3-diol-2,6 (I) by two volumes of hydrogen. 5 g of the unsaturated ketoglycol (I) were hydrogenated in 40 ml of alcohol over 0.5 g of Pt black by a quantity of hydrogen that was double the amount calculated for one double bond. The second molecule of hydrogen was added uniformly at a considerably lower rate than the first. On completion of the hydrogenation the alcohol was driven off and the remaining material distilled in vacuo. The substance obtained was colorless and was kept for a long time without any change. It was not hydrogenated over Pt black and did not form derivatives at the carbonyl group.

B.p. 68-70° (5-6 mm), n_D^{20} 1.4393, d_4^{20} 0.9106, MR_D 49.77; calc. 49.57. Found %: C 69.71, 69.77; H 11.87, 11.99. H_{act} , number 1.2, 1.3 M 173, 171. $C_{10}H_{20}O_2$. Calculated %: C 69.77; H 11.63. H_{act} , number 1 M 172.

The results obtained correspond with 2,2,5,6,6-pentamethyl-3-hydroxytetrahydropyran (VI).

Oxidation. 5.2 g of potassium permanganate were used to oxidize 3.6 g of tetrahydropyran. Acetone was separated from the neutral products and identified as the 2,4-dinitrophenylhydrazones; the saturated ketoglycol (IV), b.p. 88.5-90° was obtained and a mixed melting point with a sample of the known product (IV) showed no depression. A large quantity of CO_2 was obtained from the acid products and also a very small quantity of a crystalline acid which decolorized a $KMnO_4$ solution. The quantity was so small, however, that it was only possible to titrate one sample.

Found: Neutr. equiv. 113. $C_7H_{12}O_2$, calculated: 128.

Thus, one may assume that this acid may possibly be 3,4-dimethylheptene-3-acid which might result from the heating and dehydration of 3,4-dimethyl-3-hydroxyvalerianic acid.

The infrared spectrum of cyclic compound (VI) was taken with an LiF prism in the 2900-3800 cm^{-1} region, and with an NaCl prism in the 1560-1900 cm^{-1} region. Frequency observed: 3488 cm^{-1} (OH group joined by an intermolecular bond). Frequencies corresponding to a double bond and a carbonyl group were not observed.

Efforts were made to dehydrate the cyclic product by heating it with 10 and 20% sulfuric acid; however the substance remained unchanged which once again indicates that the hydroxyl group in this compound is secondary and not tertiary. Likewise unsuccessful was the attempt to split the cyclic product by means of hydrogen through the action of sodium in liquid ammonia.

The reaction of 2,3,6-trimethyl-5-ketoheptene-3-diol-2,6 (I) with sulfuric acid. During the course of 3.5-4 hours, 12 g of 2,3,6-trimethyl-5-ketoheptene-3-diol-2,6 were added in small portions, with vigorous stirring, to 80 ml of concentrated sulfuric acid which was cooled to -10 to -15° . Then the reaction mixture poured over finely ground ice and salted out with ammonium sulfate. This solution was extracted with ether. After drying and removing the ether, the remaining material was poured into a crystallizing dish where it crystallized. After being pressed out on a porous plate the crystals were dissolved in hot alcohol and precipitated by water. After purifying twice the yield of the product was about 50%. The melting point of the basic product was $121-122^\circ$ and that of a very small residue $158-160^\circ$. We did not succeed in absolutely purifying the product; it did not hydrogenate over Pt black, did not give derivatives at the carbonyl group, and did not decolorize a solution of potassium permanganate.

Found %: C 67.54, 67.53; H 9.80, 9.91. H_{act} number 0.91, 0.80. M 168, 171. Calculated for tetrahydrofuranone (VII) $\text{C}_{10}\text{H}_{16}\text{O}_3$, %: C 71.43; H 9.52. H_{act} number 0. M 168. Calculated for dihydropyran (VIII) $\text{C}_{10}\text{H}_{16}\text{O}_2$,

The infrared spectrum was taken with an LiF prism in the 2900-3800 cm^{-1} region and with an NaCl prism in the 1560-1900 cm^{-1} region. The following frequencies were found: 3458 cm^{-1} (OH groups joined by an intermolecular bond), 3612 cm^{-1} (free OH), 1674 and 1742 cm^{-1} (carbonyl group).

The reaction of this product with sulfuric acid. On distillation with 10% sulfuric acid, water and a small quantity of water an insoluble liquid product collected in the receptacle. This was salted out with potash and extracted with ether. After drying over Na_2SO_4 and removal of the ether, the remaining material was distilled in vacuo.

B.p. 66° (13), n_D^{20} 1.4421, d_4^{20} 0.9385 M_R^D 47.43. $\text{C}_{10}\text{H}_{16}\text{O}_2$ F, calculated: 47.32. Found %: C 71.34, 71.55; H 9.71, 9.64. $\text{C}_{10}\text{H}_{16}\text{O}_2$, Calculated %: C 71.43; H 9.52.

2,4-Dinitrophenylhydrazone, m.p. $115-116^\circ$.

Found, %: N 16.39, 16.16. $\text{C}_{16}\text{H}_{20}\text{O}_5\text{N}_4$, Calculated %: N 16.09.

The substance does not contain a hydroxyl group nor decolorize a solution of potassium permanganate.

According to the analytical data and its properties, it is 2,2,5-trimethyl-5-isopropenyl-3-ketotetrahydrofuran.

In the infrared spectrum, taken with an NaCl prism in the 1560-1900 cm^{-1} region, the 1722 cm^{-1} frequency was observed which is characteristic of the carbonyl group.

Some of the original product which did not react was recovered from the tarry residue in the distillation flask.

SUMMARY

1. The unsaturated δ -ketoglycol - 2,3,6-trimethyl-5-ketoheptene-3-diol-2,6 - was synthesized by the condensation of dimethylacetylcarbinol and its structure determined by chemical and spectroscopic methods.

2. The catalytic hydrogenation of this glycol was studied and it was shown that the saturated ketoglycol - 2,3,6-trimethyl-5-ketoheptanediol-2,6 - formed by the addition of one molecule of hydrogen, on heating during the process of separation, easily dehydrates and is converted into the unsaturated ketoalcohol - 2,3,6-trimethyl-5-ketoheptene-2-ol-6.

3. It was shown that the unsaturated δ -ketoglycol is able to add two molecules of hydrogen, the second of which adds at the double bond of the carbonyl group. The triatomic alcohol thus formed - 2,3,6-trimethylheptane-triol-2,5,6 - during the process of separation, splits off a molecule of water from the two tertiary hydroxyl groups and is converted into 2,2,5,6,6-pentamethyl-3-hydroxytetrahydropyran.

4. The ketoglycol 2,3,6,-trimethyl-5-ketoheptene-3-diol-2,6 isomerizes, on treatment with concentrated sulfuric acid at low temperature, to give 2,2,5-trimethyl-5(β -hydroxyisopropyl) tetrahydrofuranone-3, with a possible admixture of 2,2,5,6,6-pentamethyl-3-ketodihydropyran-2,3.

5. It was shown that on distillation with 16% sulfuric acid this tetrahydrofuranone dehydrates and is converted into 2,2,5-trimethyl-5-isopropenyl-3-ketotetrahydrofuran.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

TERTIARY TRIHYDRIC ALCOHOLS OF THE ACETYLENIC AND OLEFINIC SERIES AND THEIR CONVERSION REACTIONS

XXIII. OXIDATION WITH PEROXYACETIC ACID OF OLEFINIC 1,2,5-TRIOLS-2,3,6-TRIMETHYL-4-HEPTENE-2,3,6-TRIOL; 3,4,7-TRIMETHYL-5-OCTENE-3,4,7-TRIOL; 5-METHYL-2-(1-HYDROXYCYCLOHEXYL)-3-HEXENE-2,5-DIOL; and 2,4-DI(1-HYDROXYCYCLOHEXYL)-3-BUTEN-2-OL

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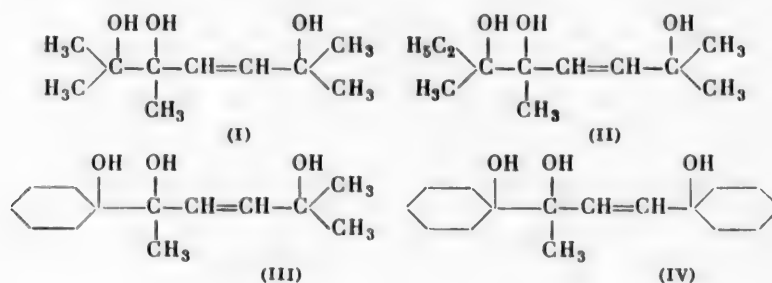
pp. 2534-2538, August, 1961

Original article submitted August 1, 1960

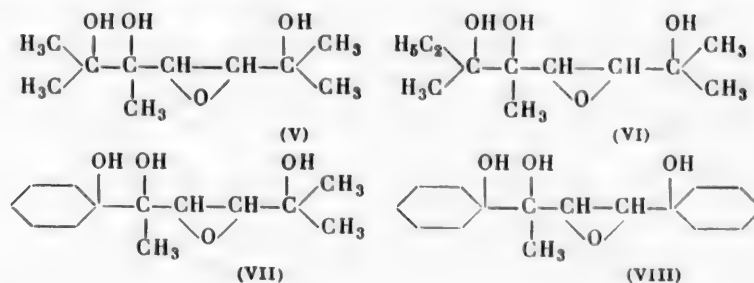
Olefinic glycerols obtained by hydrogenation of the corresponding acetylenic triols were previously described [1].

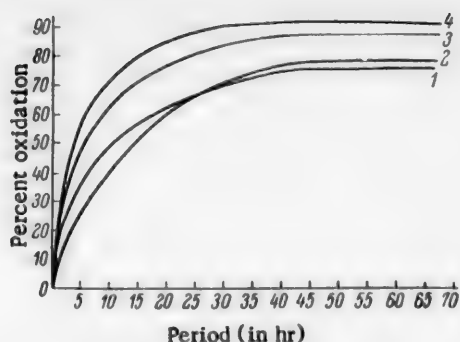
The present work was undertaken with the objective of preparation of α -oxides of olefinic triols. There is considerable literature on the preparation of α -oxides from various classes of unsaturated organic compounds. A discussion of these data is unnecessary because in the last ten years several comprehensive surveys of the field have been published [2,3]. α -Oxides containing three hydroxyl groups, however, have not previously been described, so that definite interest is attached to their synthesis.

We subjected the following olefinic triols to oxidation: 2,3,6-trimethyl-4-heptene-2,3,6-triol (I), 3,4,7-trimethyl-5-octene-3,4,7-triol (II), 5-methyl-2-(1-hydroxycyclohexyl)-3-hexene-2,5-diol (III), and 2,4-di-(1-hydroxycyclohexyl)-3-buten-2-ol (IV).



Oxidation was performed with 55-65% peroxyacetic acid [4]. In all cases the α -oxides were isolated: 2,3,6-trimethyl-4-epoxyheptane-2,3,6-triol (V); 3,4,7-trimethyl-5-epoxyoctane-3,4,7-triol (VI); 5-methyl-2-(1-hydroxycyclohexyl)-3-epoxyhexane-2,5-diol (VII); and 2,4-di-(1-hydroxycyclohexyl)-3-epoxybutan-2-ol (VIII).

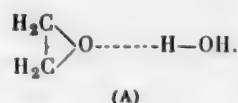




Rate of oxidation of olefinic triols by acetyl hydroperoxide. 1) 2,3,6-trimethyl-4-heptene-2,3,6-triol; 2) 3,4,7-trimethyl-5-octene-3,4,7-triol; 3) 5-methyl-2-(1-hydroxycyclohexyl)-3-hexene-2,5-diol; 4) 2,4-di-(1-hydroxycyclohexyl)3-buten-2-ol.

The speed of oxidation of each olefinic triol was determined in a special experiment [5,6]. In the curves of oxidation rate the percent of oxidation is plotted along the ordinates and the period from start of reaction along the abscissas (see figure).

The curves show that oxidation takes place to the extent of 90-92%, although the oxides could not separate completely due to their very high solubility in water. As in the case of ethylene oxide [7], we should evidently expect these oxides to form with water a hydrogen bond of type (A).



The yields of the various oxides consequently varied between 60 and 80%. The infrared absorption spectra of all the oxides that we prepared were studied with the IKS-14 spectrograph using a NaCl prism in paraffin oil*. The bands corresponded to those of a three-membered oxide ring [89].

Oxide	Absorption band	
V	840 cm^{-1}	925 cm^{-1}
VI	828 cm^{-1}	931 cm^{-1}
VII	828 cm^{-1}	922 cm^{-1}
VIII	841 cm^{-1}	905 cm^{-1}

EXPERIMENTAL

I. Oxidation of 2,3,6-trimethyl-4-heptene-2,3,6-triol (I). Trimethylheptenetriol was prepared by hydrogenation of 2,3,6-trimethyl-4-heptyne-2,3,6-triol in methyl alcohol over palladium deposited on copper. It had m.p. 116-117° (from benzene), in agreement with the literature [1].

To 4.7 g of 2,3,6-trimethyl-4-heptene-2,3,6-triol (I) in 150 ml of absolutely dry ether, mechanically stirred, was added in the course of 0.5 hr 3.43 g of 55.4% peroxyacetic acid at room temperature (24-25°). After being stirred for 30 min, the reaction mixture was allowed to stand at room temperature for 3 days. It was then neutralized with 3% aqueous NaOH solution and extracted many times with ether. The ethereal extracts were dried with calcined Na_2SO_4 . The ether was driven off and colorless crystals (1.9 g) came down; m.p. 100-101° (from ether). The aqueous layer was salted out with $(\text{NH}_4)_2\text{SO}_4$ and extracted with ether in an extractor for 80-85 hr. The crystals initially extracted (1.2 g) had m.p. 100-101°; those later extracted (0.1 g) had m.p. 116-117°.

The substance with m.p. 116-117° was unchanged 2,3,6-trimethyl-4-heptene-2,3,6-triol (I) (mixed melting test).

The crystals with m.p. 100-101° (total yield 3.1 g or 60.8%) were 2,3,6-trimethyl-4-heptene-2,3,6-triol (V).

Found %: C 58.49, 58.64; H 10.03; OH 24.75, 24.67. M 210.5, 208.2 (Rast method) $\text{C}_{10}\text{H}_{20}\text{O}_4$. Calculated %: C 58.83; H 9.799; OH 25.00 M 204. Infrared absorption bands: 840, 928 cm^{-1} .

Study of rate of oxidation of trimethylheptenetriol (I). To 4.7 g of heptenetriol, dissolved in 150 ml of absolute ether, was added 3.43 g of 55.47% peroxyacetic acid at $20 \pm 2^\circ$. The progress of oxidation was checked from time to time by sampling. The percentage of peroxyacetic acid in the sample was determined by titration with 0.1 N $\text{Na}_2\text{S}_2\text{O}_3$ solution. A blank was run at the same time.

*The spectra were prepared by the laboratory of the Institute of Polymer Chemistry of the Academy of Sciences of the Uzbek SSR to whom the authors convey their deep appreciation.

Type of experiment	Number of milliliters of 0.1 N $\text{Na}_2\text{S}_2\text{O}_3$ consumed for titration of unreacted peroxyacetic acid after (hr):							
	0	3	6	18	30	42	54	66
Main	0.76	0.62	0.45	0.31	0.23	0.18	0.18	0.18
Blank	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76

Nature of experiments	Number of milliliters of 0.1N $\text{Na}_2\text{S}_2\text{O}_3$ consumed for titration of unreacted peroxyacetic acid after (hr):								
	0	3	6	18	30	42	54	66	78
Main	0.76	0.60	0.44	0.30	0.23	0.17	0.17	0.17	0.17
Blank	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76

Nature of experiment	Number of milliliters of 0.1 n $\text{Na}_2\text{S}_2\text{O}_3$ consumed for titration of unreacted peroxyacetic acid after (hr):									
	0	0.5	1	2	5	8	20	32	44	56
Main	0.77	0.56	0.52	0.41	0.31	0.21	0.15	0.11	0.09	0.09
Blank	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77

Nature of experiment	Number of milliliters of 0.1 N $\text{Na}_2\text{S}_2\text{O}_3$ consumed for titration of unreacted peroxyacetic acid after (hr):									
	0	0.5	1	2	5	8	20	32	44	56
Main	0.77	0.62	0.58	0.50	0.33	0.25	0.16	0.08	0.06	0.06
Blank	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77	0.77

II. Oxidation of 3,4,7-trimethyl-5-octene-3,4,7-triol (II). Trimethyloctenetriol was prepared by hydrogenation of 3,4,7-trimethyl-5-octyne-3,4,7-triol in methanol on palladium deposited on copper. It had b.p. 117-118° (2 mm) and n_D^{20} 1.4774 in agreement with the literature [1].

Oxidation of 10 g of 3,4,7-trimethyl-5-octene-3,4,7-triol, dissolved in 125 ml of absolute ether, was effected at 20° with 6 g of 70% peroxyacetic acid which was added in the course of 50 min. After it had been stirred for half an hour, the reaction mixture was allowed to stand for 72 hr at room temperature (20-22°). The oxidation product was worked up as in the preceding experiment. Extraction of the aqueous portion at first gave crystals with m.p. 107-108°, followed by 1.7 g of liquid with b.p. 117-118° (2 mm), n_D^{12} 1.4774, which corresponded to the initial 3,4,7-trimethyl-5-octene-3,4,7-triol.

The yield of crystals with m.p. 107-108° was 6.1 g (68%); they were 3,4,7-trimethyl-5-epoxyoctane-3,4,7-triol (VI).

Found %: C 60.87, 60.37; H 10.29, 10.23; OH 23.04, 22.67. $\text{C}_{11}\text{H}_{22}\text{O}_4$. Calculated %: C 60.54; H 10.09; OH 23.4. Infrared absorption bands: 828, 931 cm^{-1} .

Study of rate of oxidation of trimethyloctenetriol (II). To 5.05 g of triol, dissolved in 150 ml of dry ether, was added 3.43 g of 55.47% peroxyacetic acid. The experiment was checked as before.

III. Oxidation of 5-methyl-2-(1-hydroxycyclohexyl)-3-hexene-2,5-diol (III). The triol was synthesized by hydrogenation of 5-methyl-2-(1-hydroxycyclohexyl)-3-hexyne-2,5-diol in methanol over palladium deposited on copper. It melted at 102-103° in agreement with the literature [1].

To 20 g of 5-methyl-2-(1-hydroxycyclohexyl)-3-hexene-2,5-diol in 150 ml of anhydrous ether at 18-20° was added, with vigorous mechanical stirring, 20 g of 65% peroxyacetic acid in the course of 2.5 hr. After about 30-35 min the reaction mixture became cloudy and began to deposit white crystals. The mixture was allowed to stand for 48 hr. There was obtained 12.1 g of fine, white crystals with m.p. 151.5-152.5° (from benzene) consisting of 5-methyl-2-(1-hydroxycyclohexyl)-3-epoxyhexane-2,5-diol (VII). Ether extraction of the filtrate gave a further 2.2 g of crystals with m.p. 151.5-152.5° and 1.9 g of original diol. The total yield of 5-methyl-2-(1-hydroxycyclohexyl)-3-epoxyhexane-2,5-diol was 14.3 g (74.0%).

Found %: C 63.60, 63.63; H 9.95, 9.93; OH 20.23, 20.20. M 254.9, 260.2 (Rast's method). $C_{13}H_{24}O_4$. Calculated %: C 63.93; H 9.84; OH 20.90. M 244. Infrared absorption bands: 818, 922 cm^{-1} .

Study of rate of oxidation of triol (III). To 5.7 g of triol, dissolved in 150 ml of absolute ether, was added 3.46 g of 54.82% peroxyacetic acid. The experiment was checked as before.

IV. Oxidation of 2,4-di-(1-hydroxycyclohexyl)-3-buten-2-ol (IV). 2,4-Di-(1-hydroxycyclohexyl)-3-buten-2-ol was prepared by hydrogenation of 2,4-di-(1-hydroxycyclohexyl)-3-buten-2-ol and had m.p. 111-112° in agreement with the literature [1].

Oxidation of 10 g of 2,4-di-(1-hydroxycyclohexyl)-3-buten-2-ol was carried out with 10 g of 65% peroxyacetic acid. After stirring for 30 min (after addition of the whole of the peroxyacetic acid), crystals with m.p. 146-147° (from a large volume of benzene) began to come down. There was isolated 9.2 g (86.8%) of 2,4-di-(1-hydroxycyclohexyl)-3-epoxybutan-2-ol (VIII).

Found %: C 68.03, 67.36; H 10.02, 10.14; OH 18.68, 18.46. $C_{16}H_{28}O_4$. Calculated %: C 67.61; H 9.86; OH 17.94. Absorption bands in the infrared spectrum: 841, 905 cm^{-1} .

Study of the rate of oxidation of substance (IV). Oxidation of 6.7 g of (IV) in 150 ml of absolute ether was effected with 3.4 g of 54.82% peroxyacetic acid. The rate of oxidation was followed as before.

SUMMARY

1. The oxidation with peroxyacetic acid of four olefinic triols was studied: 2,3,6-trimethyl-4-heptene-2,3,6-triol; 3,4,7-trimethyl-5-octene-3,4,7-triol; 5-methyl-2-(1-hydroxycyclohexyl)-3-hexene-2,5-diol; and 2,4-di-(1-hydroxycyclohexyl)-3-buten-2-ol.

2. It was shown that oxidation leads to good yields of α -oxides of olefinic triols. The presence of oxide rings was verified by the infrared absorption spectra.

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TERTIARY TRIHYDRIC ALCOHOLS OF THE ACETYLENIC AND OLEFINIC SERIES AND THEIR CONVERSION REACTIONS

XXIV. OXIDATION WITH PEROXYACETIC ACID OF 1,2,5-TRIOLS OF THE OLEFINIC
SERIES - 2,3,6-TRIMETHYL-4-OCTENE-2,3,6-TRIOL; 3,4,7-TRIMETHYL-5-NONENE-
3,4,7-TRIOL; AND 5-METHYL-2-(1-HYDROXYCYCLOPENTYL)-3-HEXENE-2,5-DIOL

V. I. Nikitin and M. M. Tulyaganov

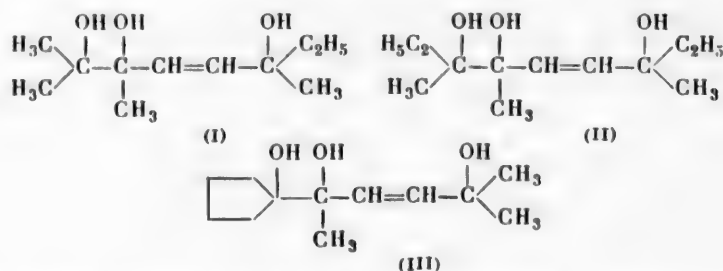
Institute of Chemistry of the Academy of Sciences of the Tadjik SSR

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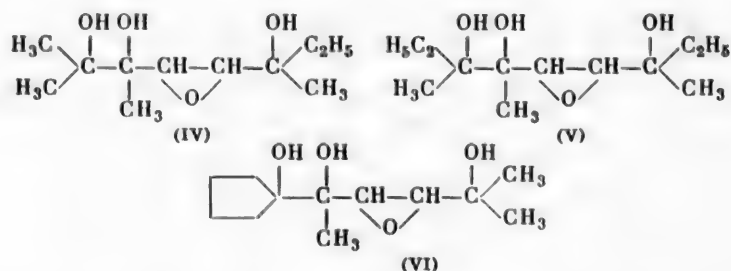
pp. 2538-2541, August 1961

Original article submitted September 2, 1960

In the preceding paper [1] we described the preparation of α -oxides of some 1,2,5-triols of the olefinic series by oxidation of the triols themselves with peroxyacetic acid. In view of the potential chemical and synthetic interest of epoxytriols, we decided to extend the range of this series of compounds by subjecting several more olefinic 1,2,5-triols to oxidation with peroxyacetic acid. With this objective we subjected the following compounds to oxidation in the present work: 2,3,6-trimethyl-4-octene-2,3,6-triol (I) [2]; 3,4,7-trimethyl-5-nonene-3,4,7-triol (II) [2]; and 5-methyl-2-(1-hydroxycyclopentyl)-3-hexene-2,5-diol (III) [3].



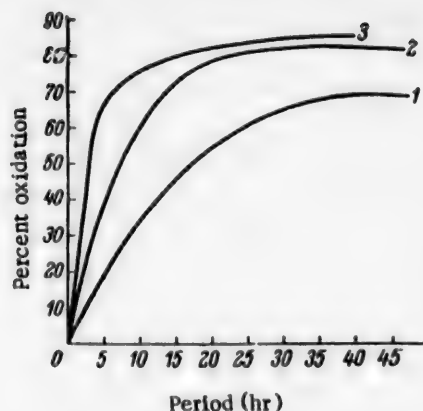
Oxidation led to isolation in yields of 60 to 73% of the corresponding α -oxides (epoxytriols): 2,3,6-trimethyl-4-epoxyoctane-2,3,6-triol (IV); 3,4,7-trimethyl-5-epoxynonane-3,4,7-triol (V); and 5-methyl-2-(1-hydroxycyclopentyl)-3-epoxyhexane-2,5-diol (VI).



The rate of oxidation of the olefinic triols was studied and oxidation rate curves were plotted (see figure).

We see from the curves that the olefinic triols were oxidized to the extent of 70-86%; due, however, to the high solubility in water, the whole of the oxide formed could not be extracted, so that the yield was lowered.

As in the case of olefinic hydrocarbons [4], the rate of oxidation of 1,2,5-triols of the olefinic series depends on the molecular weight of the triol and on the nature of the substituting radicals.



Rate of oxidation with peroxyacetic acid.

- 1) 2,3,6-trimethyl-4-octene-2,3,6-triol;
- 2) 3,4,7-trimethyl-5-nonene-3,4,7-triol;
- 3) 5-methyl-2-(1-hydroxycyclopentyl)-3-hexene-2,5-diol.

The structure of the 4-epoxy-1,2,5-triols was confirmed by the infrared absorption spectra* taken with the IKS-14 spectrograph using a NaCl prism in paraffin oil. The spectra of the α -oxides contained absorption bands characteristic of a three-membered oxide ring [5].

EXPERIMENTAL

1. Oxidation of 2,3,6-Trimethyl-4-octene-2,3,6-triol (I)

The triol was prepared by hydrogenation of 2,3,6-trimethyl-4-octyne-2,3,6-triol and had b.p. 114-116° (2 mm), n_D^{20} 1.4757 [2].

To 20 g of 2,3,6-trimethyl-4-octene-2,3,6-triol (I) in 500 ml of absolute ether, stirred mechanically, was added at room temperature (24-25°) 15 g of 48.74% peroxyacetic acid in the course of an hour. No rise in temperature of the reaction mixture was observed during the operation. Stirring was continued for 8 hr, and then the mixture was allowed to stand for five days. After completion of the reaction, the reaction mixture was neutralized with 5% aqueous NaOH solution, and then extracted 6-7 times with ether. The ethereal extracts were united and dried over sodium sulfate, after which the ether was distilled off and the product fractionated *in vacuo*. Several distillations gave 9.4 g of substance with b.p. 170-171° (6 mm). This was 2,3,6-trimethyl-4-epoxyoctane-2,3,6-triol (V), which has not previously been described.

Ether extraction of the aqueous layer for ten days yielded a further 3.7 g of 2,3,6-trimethyl-4-epoxy-2,3,6-triol (IV) in the form of a poorly mobile, viscous liquid. Total yield 13.1 g (60.7%).

B.p. 170-171° (6 mm), n_D^{20} 1.4758, d_4^{20} 1.0587, M_{rD} 56.92; calc. 57.71. Found%: C 60.44, 60.47; H 10.52, 10.30; OH 24.46, 24.12. $C_{11}H_{22}O_4$. Calculated %: C 60.54; H 10.29; OH 23.40.

Study of oxidation rate. To 5.05 g of octenetriol (I), dissolved in 150 ml of absolute ether, was added 3.67 g of 68% peroxyacetic acid. The experiment was run at $25 \pm 2^\circ$. The progress of oxidation was followed by analysis of samples at intervals. The percentage of peroxyacetic acid in the sample was determined by titration with 0.1 N $Na_2S_2O_3$ solution. A blank experiment was run under the same conditions (Table 1).

TABLE 1

Nature of experiment	Number of milliliters of 0.1 N $Na_2S_2O_3$ consumed for titration of unreacted peroxyacetic acid								
	Duration (in hr)								
	0	12	24	36	48	60	72	84	96
Main	6.64	5.20	4.40	3.20	2.80	2.30	2.10	2.0	2.0
Blank	6.64	6.64	6.64	6.64	6.64	6.64	6.64	6.64	6.64

2. Oxidation of 3,4,7-Trimethyl-5-nonene-3,4,7-triol (II)

The triol was prepared by hydrogenation of 3,4,7-trimethyl-5-nonyne-3,4,7-triol and had b.p. 126-127° (2 mm) and n_D^{20} 1.4790, in agreement with the literature [2].

Oxidation of 20 g of the triol, dissolved in 500 ml of absolute ether, was performed for 70 min at 20-22° with 15 g of 49.70% peroxyacetic acid by the preceding procedure. After it had been stirred for 0.5 hr, the mixture was

*The spectra were determined at the laboratory of the Institute of Polymer Chemistry of the Academy of Sciences of the Uzbek SSR to whom we express our sincere thanks.

allowed to stand for five days at room temperature (20-22°). The product was further worked up as described above. After the greater part of the ether had been distilled off, the residue soon deposited white crystals. Numerous recrystallizations gave 15.8 g (73.55%) of 3,4,7-trimethyl-5-epoxynonane-3,4,7-triol (V), m.p. 108-109° (from ligroine).

Found %: C 62.09, 62.22; H 10.15, 10.29; OH 22.17, 21.59. $C_{12}H_{24}O_4$. Calculated %: C 62.06; H 10.34; OH 21.96. Absorption bands in infrared spectrum: 826, 925 cm^{-1} .

TABLE 2

Nature of experiment	Number of milliliters of 0.1 N $Na_2S_2O_3$ consumed for titration of unreacted peroxyacetic acid								
	Duration (in hr)								
	0	12	24	36	48	60	72	84	96
Main	6.64	3.60	2.10	1.50	1.20	1.20	1.20	1.20	1.20
Blank	6.64	6.64	6.64	6.64	6.64	6.64	6.64	6.64	6.64

Study of oxidation rate. To 5.4 g of nonenetriol (II), dissolved in 150 ml of dry ether, was added 3.67 g of 51.68% peroxyacetic acid. The course of oxidation was followed as before (Table 2).

3. Oxidation of 5-methyl-2-(1-hydroxycyclopentyl)-3-hexene-2,5-diol (III)

The triol was prepared by hydrogenation of 5-methyl-2-(1-hydroxycyclopentyl)-3-hexyne-2,5-diol and had m.p. 113-114.5° [3].

Oxidation of 20 g of 5-methyl-2-(1-hydroxycyclopentyl)-3-hexene-2,5-diol was effected with 16 g of 48.7% peroxyacetic acid. The reaction was performed with periodic stirring for five days at room temperature. The mixture was worked up as in the first two preparations and 15.2 g (70.81%) of product was isolated in the form of fine crystals. Repeated recrystallizations gave large rhombohedral crystals of 5-methyl-2-(1-hydroxycyclopentyl)-3-epoxyhexane-2,5-diol (VI) with m.p. 102-103° (from absolute ether).

Absorption bands in the infrared: 831, 925 cm^{-1} . Found %: C 62.75, 62.86; H 9.59, 9.28; OH 21.30, 21.11 $C_{12}H_{22}O_4$. Calculated %: C 62.60, H 9.56; OH 22.17.

Study of oxidation rate. Reaction components were 5.35 g of triol (in 150 ml of absolute ether) and 3.67 g of 51.68% peroxyacetic acid. The rate of oxidation was followed as before (Table 3).

TABLE 3

Nature of experiment	Number of milliliters of 0.1 N $Na_2S_2O_3$ consumed for titration of unreacted peroxyacetic acid							
	Duration (hr)							
	0	7	19	31	43	55	67	80
Main	6.64	2.64	1.60	1.32	1.13	1.00	1.00	1.00
Blank	6.64	6.64	6.64	6.64	6.64	6.64	6.64	6.64

SUMMARY

1. The following olefinic triols were oxidized with peroxyacetic acid: 2,3,6-trimethyl-4-octene-2,3,6-triol; 3,4,7-trimethyl-5-nonene-3,4,7-triol; and 5-methyl-2-(1-hydroxycyclopentyl)-3-hexene-2,5-diol.

2. It was shown, in complete agreement with earlier data, that oxidation of olefinic triols with peroxyacetic acid leads to formation of the corresponding α -oxides.

3. The following α -oxides were obtained: 2,3,6-trimethyl-4-epoxyoctane-2,3,6-triol; 3,4,7-trimethyl-4-epoxynonane-3,4,7-triol; and 5-methyl-2-(1-hydroxycyclopentyl)-3-epoxybutane-2,5-diol.

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PROPERTIES OF 4-HYDROXYMETHYLENE-2,2,5,5-TETRAALKYL-3-FURANIDONES

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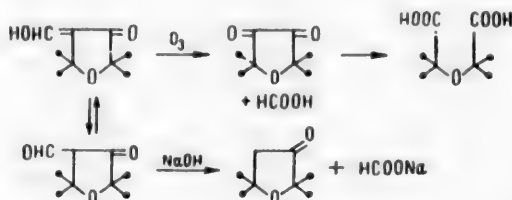
pp. 2542-2548, August, 1961

Original article submitted August 8, 1960

In one of the preceding investigations [1] it was shown that condensation of 2,2,5,5-tetraalkyl-3-furanidones with ethyl formate is a convenient method of synthesis of 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidones - compounds which are highly enolized and capable of forming both C- and O- derivatives.

In the present work we continued the study of the properties of these β -ketoaldehydes of the tetrahydrofuran series with reference to their ozonolysis, ketonic cleavage, reactions with ammonia, diethylamine, and thionyl chloride, and also methylation with diazomethane and methyl iodide.

Treatment with ozone of 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone gave 2,2,5,5-tetramethyl-3,4-furanidinedione, tetramethyldiglycolic acid, and formic acid; consequently the primary reaction product is 2,2,5,5-tetramethyl-3,4-furanidinedione which is subsequently oxidized to tetramethyldiglycolic acid. * Hence it follows that enolization of 4-formyl-2,2,5,5-tetraalkyl-3-furanidones proceeds preferentially at the aldehyde group, and the tautomeric form of these compounds is 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidones, in harmony with data for the enolization of hydroxymethyl ketones of the alicyclic series [2] and of 4-acetyl-2,2,5,5-tetramethyl-



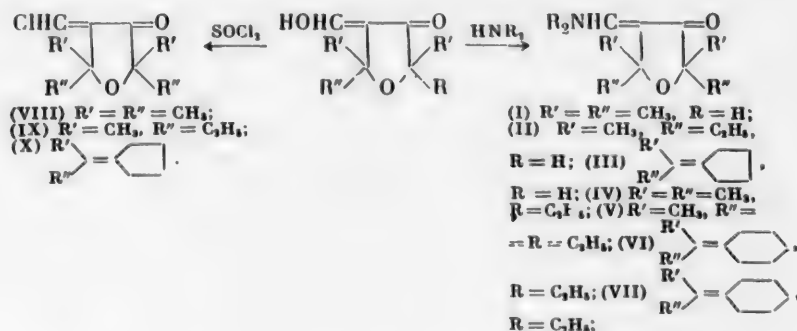
In studies of the behavior of 4-hydroxymethylene-2,2,5,5-tetramethyl- and 2,5-dimethyl-2,5-diethyl-3-furanidones we established that their ketonic cleavage takes place under conditions more drastic than in the case of aliphatic and alicyclic hydroxymethylene ketones. Hydroxymethylenemethyl propyl ketone, for example, is cleaved [4] by cold caustic alkali to methyl propyl ketone and formic acid, whereas 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidones are stable under these conditions and undergo decomposition only after boiling for 5 hr with 15% sodium hydroxide solution.

A characteristic feature of hydroxymethylene ketones is the high reactivity of the hydroxyl group which is replaced with facility by the amino group [4-6] and by halogen [7]. In chloroform solution 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidones smoothly react in the cold with ammonia to give 4-aminomethylene-2,2,5,5-tetraalkyl-3-furanidones (I-III) in yields of 90-97%. In alcoholic solution they react with diethylamine to give 4-diethylaminomethylene-2,2,5,5-tetraalkyl-3-furanidones (IV-VII) in 55-80% yields. Compounds (IV and V) are oily liquids with the high exaltation (by 4-5 units) of refraction characteristic of this class of compounds [8].

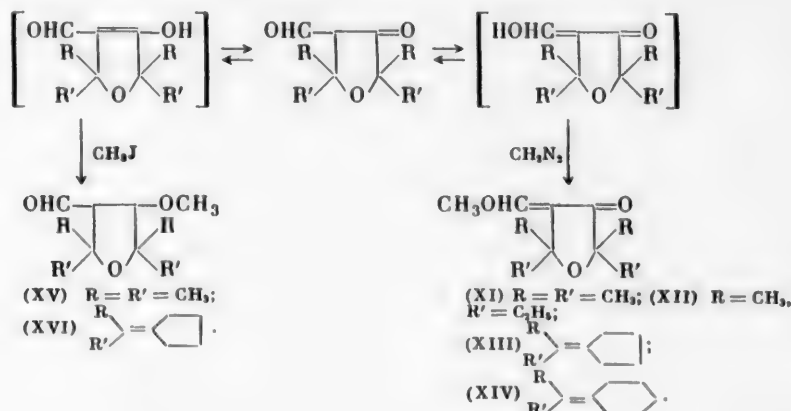
*Oxidation of 2,2,5,5-tetramethyl-3,4-furanidinedione by ozone to tetramethyldiglycolic acid was described earlier [3].

All these aminomethylene ketones of the tetrahydrofuran series give a deep red color with ferric chloride solution; this effect is specific for β -aminovinyl ketones [9]*.

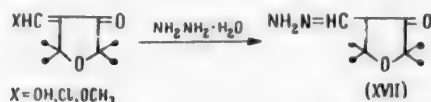
4-Chloromethylene-2,2,5,5-tetraalkyl-3-furanidones (VIII-X) are obtained in 64-87% yields by reaction of 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidones with thionyl chloride. These products all quickly decompose in the air; they are strong lachrymators and irritate the skin.



4-Hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidones react smoothly with an ethereal solution of diazomethane to give high yields (73-94%) of the corresponding O-methyl esters - 4-methoxymethylene-2,2,5,5-tetramethyl-3-furanidones (XI-XIV).



All the methyl ethers (XI-XIV) are unstable; their structure was confirmed in the case of (XI) by hydrolysis with 10% hydrochloric acid to give 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone (yield 74%), and by reaction with hydrazine to give a stable hydrazone (XVII) identical with the hydrazone prepared from 4-hydroxymethylene- and 4-chloromethylene-2,2,5,5-tetramethyl-3-furanidone.



An unexpected result was obtained when we methylated 4-formyl-2,2,5,5-tetraalkyl-3-furanidones with methyl iodide in presence of potassium carbonate in acetone solution: We isolated compounds (XV & XVI) which are different from ethers (XI & XIII) and are not C-derivatives of 4-formyl-2,2,5,5-tetraalkyl-3-furanidones as was to be expected on the basis of literature analogies [10]. Compounds (XV & XVI) possess the same empirical formulas as ethers

*The 4-aminomethylene-2,2,5,5-tetraalkyl-3-furanidones (I, II, VI) were isolated in the form of stable monohydrates.

(XI & XIII). Hydrolysis of (XV) with 10% hydrochloric acid gives 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone (yield 66.5%), while reaction with hydrazine gives an unstable substance which spontaneously cyclizes to a furanidinopyrazole in the course of a few hours.

In the light of the foregoing facts, we may suggest that methylation of 4-formyl-2,2,5,5-tetraalkyl-3-furanidones with methyl iodide in acetone in presence of potassium carbonate is accompanied by enolization of the initial β -ketoaldehyde on the side of the ketonic group, and the resulting hydroxyl is methylated by methyl iodide so that the end products are 3-methoxy-4-formyl-2,2,5,5-tetraalkyldihydrofurans (XV & XVI).

EXPERIMENTAL

Ozonization of 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone. A rapid stream of 4% ozone was passed for 4 hr into a solution (cooled to 0°) of 3.4 g of 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone in 60 ml of carbon tetrachloride. The crimson solution was left for 2 hr at room temperature; the solvent was evaporated in vacuo, and the residue decomposed by boiling with 30 ml of water for 3.5 hr. The solution was then made alkaline with saturated sodium carbonate solution to pH 12 and extracted with hot benzene for 15 hr in an extractor. The benzene was distilled off and the residue treated with phenylhydrazine in acetic acid solution to give the phenylhydrazone of 2,2,5,5-tetramethyl-3,4-furanidinedione with m.p. 95-96° (from alcohol) [3].

The alkaline solution was evaporated to a volume of 30 ml, acidified with concentrated hydrochloric acid, and extracted with benzene. Removal of the benzene left 2 g (54%) of tetramethyldiglycolic acid with m.p. 153-155° (from chloroform) [3]. Part of the aqueous solution was made alkaline and mercuric chloride was added. Mercurous chloride came down, thereby confirming the presence of formic acid in the solution.

Hydrolysis of 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidones. A mixture of 0.02 mole of 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidone and 25 ml of 15% aqueous sodium hydroxide solution was boiled for 5 hr (until the reaction with ferric chloride was negative), and then distilled with steam. The distillate was saturated with potassium carbonate, extracted with ether, and dried with magnesium sulfate. 2,2,5,5-Tetraalkyl-3-furanidone was isolated after distillation of the solvent. From 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone was obtained 1.5 g (53.5%) of 2,2,5,5-tetramethyl-3-furanidone with b.p. 147-148°; n_D^{20} 1.4200; the semicarbazone had m.p. 188-189°.

Literature data: b.p. 149-149.5°; n_D^{20} 1.4202 [11]; semicarbazone: m.p. 190° [12].

From 4-hydroxymethylene-2,5-dimethyl-2,5-diethyl-3-furanidone was obtained 1.7 g (50%) of 2,5-dimethyl-2,5-diethyl-3-furanidone, b.p. 191-192°; n_D^{20} 1.4380; semicarbazone, m.p. 136-137°.

Literature data: b.p. 90-91° (25mm); n_D^{20} 1.4383 [11]; semicarbazone, m.p. 136-138° [12].

4-Aminomethylene-2,2,5,5-tetraalkyl-3-furanidones were prepared by passing a rapid stream of dry ammonia into a solution (cooled with ice water) of 0.022 mole of 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidone in 60 ml of chloroform. A white precipitate came down and was crystallized from a mixture of absolute alcohol and ligroine.

4-Diethylaminomethylene-2,2,5,5-tetraalkyl-3-furanidones were prepared by addition of 0.06 mole of diethylamine to a solution of 0.03 mole of 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidone in 10 ml of anhydrous alcohol. The mixture was allowed to stand overnight. Unchanged substances were distilled off and the residue (in the case of compounds IV and V) distilled; compounds (VI & VII) were purified by crystallization from a mixture of ligroine and chloroform. Constants and yields of 4-aminomethylene- and 4-diethylaminomethylene-3-furanidones are set forth in Table 1.

4-Chloromethylene-2,2,5,5-tetramethyl-3-furanidone (VIII). To 8 g of 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone was added 6 g of thionyl chloride dropwise with stirring and cooling with ice and salt. After the violent reaction, the mixture was held at room temperature for an hour and the crystals were collected. Yield 7.1 g (80%), m.p. 81° (from ethanol).

Found %: C 57.45, 57.37; H 7.06, 7.06. $C_9H_{13}O_2Cl$. Calculated %: C 57.29; H 6.94.

4-Chloromethylene-2,5-dimethyl-2,5-diethyl-3-furanidone (IX). To 8 g of 4-hydroxymethylene-2,5-dimethyl-2,5-diethyl-3-furanidone was added 6 g of thionyl chloride under the above conditions. The mass was distilled in vacuo two hr after evolution of hydrogen chloride had ceased. Yield 6.2 g (71%).

TABLE 1. 4-Aminomethylene- and 4-Diethylaminomethylene-3-furanidones.

Name of substance and empirical formula	M.p.	Yield %	Found, %			Calculated, %		
			C	H	N	C	H	N
4-Aminomethylene-2,2,5,5-tetra- methyl-3-furanidone $C_8H_{15}O_2N \cdot H_2O$ (I)	104—105°	89	58.22, 58.04	8.87, 8.92	—	57.73	9.15	—
4-Aminomethylene-2,5-dimethyl- 2,5-diethyl-3-furanidone $C_{11}H_{19}O_2N \cdot H_2O$ (II)	109—110	94	61.25, 61.44	9.95, 9.93	6.22, 6.35	61.37	9.83	6.51
4-Aminomethylene-2,2,5,5-bis- pentamethylene-3-furanidone $C_{15}H_{23}O_2N$ (III)	152—153	97	71.70, 71.69	9.24, 9.05	—	72.25	9.29	—
4-Diethylaminomethylene-2,2,5,5- tetramethyl-3-furanidone $C_{13}H_{23}O_2N$ (IV) *	—	70	68.88, 68.77	10.62, 10.35	5.82, 6.03	69.28	10.29	6.20
4-Diethylaminomethylene-2,5- dimethyl-2,5-diethyl-3- furanidone $C_{15}H_{27}O_2N$ (V) **	—	54.5	—	—	5.77, 5.57	—	—	5.53
4-Diethylaminomethylene-2,2,5,5-bis- tetramethylene-3-furanidone $C_{17}H_{27}O_2N \cdot H_2O$ (VI)	83.5—84.5	77	—	—	4.34, 4.53	—	—	4.74
4-Diethylaminomethylene-2,2,5,5- bis-pentamethylene-3- furanidone $C_{19}H_{31}O_2N$ (VII)	90—91	80	—	—	4.34, 4.44	—	—	4.58

B.p. 90–91° (7 mm) n_D^{20} 1.4792, d_4^{20} 1.1200. Found %: C 61.59, 61.53; H 8.19, 8.33. $C_{11}H_{17}O_2Cl$. Calculated %: C 60.99; H 7.91.

4-Chloromethylene-2,2,5,5-bis-tetramethylene-3-furanidone (X). To 4 g of 4-hydroxymethylene-2,2,5,5-bis-tetramethylene-3-furanidone in 60 ml of ether was added 3 g of thionyl chloride with stirring, and the mixture heated to boiling on a water bath for an hour. The ether was driven off and the residue distilled in vacuo. Yield 2.95 g (67%).

B.p. 109–111° (2 mm) n_D^{20} 1.5219, d_4^{20} 1.1704, MR_D 62.72. $C_{13}H_{17}O_2ClF$. Calculated 61.69; + EMR_D 1.03. Found %: C 65.21, 65.33; H 7.09, 7.14. $C_{13}H_{17}O_2$. Calculated %: C 64.81; H 7.12.

4-Methoxymethylene-2,2,5,5-tetraalkyl-3-furanidones. To a solution of 0.04 mole of 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidone in 25–30 ml of absolute ether was added 100 ml of ethereal solution of diazomethane (containing 0.06 mole of diazomethane) in small portions with stirring and ice water cooling. After removal of the ether, the residue was distilled in vacuo in a nitrogen stream.

3-Methoxy-4-formyl-2,2,5,5-tetraalkyldihydrofurans. A mixture of equimolar quantities of 4-formyl-2,2,5,5-tetraalkyl-3-furanidone and calcined potassium carbonate was boiled for 5 hr with 100 ml of acetone and excess (50%) of methyl iodide. The cooled mass was diluted with absolute ether, the potassium carbonate separated, the solvents distilled off, and the residue recrystallized from ligroine.

Constants and yields of 4-methoxymethylene-2,2,5,5-tetraalkyl-3-furanidones and 3-methoxy-4-formyl-2,2,5,5-tetraalkyldihydrofurans are set forth in Table 2.

Hydrolysis of 4-methoxymethylene-2,2,5,5-tetramethyl-3-furanidone (XI). A mixture of 0.5 g of ether (XI) and 10 ml of 10% hydrochloric acid was shaken for 20 min. A voluminous precipitate came down. Yield of 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone 0.34 g (74%); m.p. 73–74° (from ligroine) [1]. A mixture with authentic 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone did not exhibit a depression of melting point.

*B.p. 113–114° (2 mm), n_D^{20} 1.5200, d_4^{20} 0.9723, MR_D 70.45. $C_{13}H_{23}O_2NF$. Calculated 65.16; + EMR_D 5.29.

**B.p. 134–135° (3 mm) n_D^{20} 1.5190, d_4^{20} 0.9710, MR_D 79.21. $C_{15}H_{27}O_2NF$. Calculated 74.39; EMR_D 4.82.

TABLE 2. 4-Methoxymethylene-2,2,5,5-tetraalkyl-3-furanidones and 3-Methoxy-4-formyl 2,2,5,5-tetramethyldihydrofurans

Name of substance and empirical formula	M.p.	B.p. (pressure in mm)	Yield %	Found, %		Calc., %	
				C	H	C	H
4-Methoxymethylene-2,2,5,5-tetramethyl-3-furanidone $C_{10}H_{16}O_3$ (XI)	30°	98—99 (5 mm)	80	65.06	8.89	65.19	8.75
4-Methoxy-4-formyl-2,2,5,5-tetramethyldihydrofuran $C_{10}H_{16}O_3$ (XV)	50—50.5	—	70.8	65.25, 65.26	8.77, 8.72	65.19	8.75
4-Methoxymethylene-2,5-dimethyl-2,5-diethyl-3-furanidone $C_{12}H_{20}O_3$ (XII) *	—	88—89 (4 mm)	84	68.12, 67.94	9.64, 9.49	67.89	9.50
4-Methoxymethylene-2,2,5,5-bis-tetramethylene-3-furanidone $C_{14}H_{20}O_3$ (XIII)	55—56	162—164 (7 mm)	73	71.06, 70.96	8.65, 8.59	71.16	8.53
3-Methoxy-4-formyl-2,2,5,5-bis-tetramethylenedihydrofuran $C_{14}H_{20}O_3$ (XVI)	81—82	—	36	71.29, 71.11	7.93, 8.12	71.16	8.53
4-Methoxymethylene-2,2,5,5-bis-pentamethylene-3-furanidone $C_{16}H_{24}O_3$ (XIV)	134.5—135.5 (decomp.)	—	94	72.34	9.23	72.68	9.15

Hydrazone of 4-formyl-2,2,5,5-tetramethyl-3-furanidone (XVII). a) To a solution of 1.5 g of 4-methoxy-methylene-2,2,5,5-tetramethyl-3-furanidone in 30 ml of ether was added 1 g of hydrazine hydrate; the mixture was boiled on a water bath for 20-30 min, and the ether distilled off. Yield of hydrazone 1.45 g (97%); m.p. 110-111° (from ligroine).

Found %: C 58.75, 58.66; H 8.86, 8.80; N 15.54, 15.57. $C_9H_{16}O_2N_2$. Calculated %: C 58.68; H 8.75; N 15.21.

b) Reaction of 3.4 g of 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone with 2 g of hydrazine hydrate in 30 ml of ether under the conditions of exp. a gave 3.6 g (98.5%); m.p. 110-111° (from ligroine).

c) Into a solution of 3.6 g of 4-chloromethylene-2,2,5,5-tetramethyl-3-furanidone in 40 ml of ether was stirred 2 g of hydrazine hydrate. The mixture was boiled for an hour and the ether distilled off. Yield 3.48 g (97.6%); m.p. 109-110° (from ligroine).

No depressions of melting point were observed in mixed melting tests of hydrazones (XVII) prepared in exps. a), b) and c).

Hydrolysis of 3-methoxy-4-formyl-2,2,5,5-tetramethyldihydrofuran (XV). A mixture of 3 g of ether (XV) and 15 ml of 10% hydrochloric acid was shaken for 10 min. A voluminous precipitate appeared. Yield 1.85 g (66.5%) of 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone; m.p. 73-74° (from ligroine). No depression of melting point in admixture with authentic 4-hydroxymethylene-2,2,5,5-tetramethyl-3-furanidone.

Reaction of 3-methoxy-4-formyl-2,2,5,5-tetramethyldihydrofuran (XV) with hydrazine hydrate. A mixture of 1.84 g of ether (XV), 50 ml of ether, and 1.0 g of hydrazine hydrate was heated for 30 min on a water bath, and the ether was evaporated; the residue melted at 113-114°, then solidified, and melted again at 219°. M.p. 222-223° (from aqueous alcohol). The product is 3,4-(4,5')-2',2',5', 5'-tetramethyl-3',4'-furanidinopyrazole.

SUMMARY

1. It was shown that the hydroxyl group of 4-hydroxymethylene-2,2,5,5-tetraalkyl-3-furanidones is easily replaced by amino and diethylamino groups and by chlorine.

2. Depending on the reaction conditions, methylation of 4-formyl-2,2,5,5-tetraalkyl-3-furanidones may proceed both at the enolized aldehydic group (under the action of diazomethane) and at the enolized ketonic group during methylation with methyl iodide in acetone in presence of potassium carbonate.

* n_D^{20} 1.4810, d_4^{20} 1.0080, M_{PD} 59.93. $C_{12}H_{20}O_3F$. Calculated 58.25.

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FURANIDINO BENZOPYRILIUM SALTS

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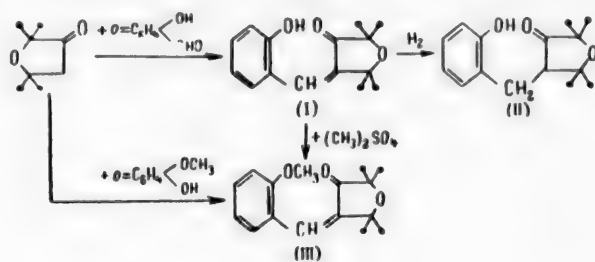
Original article submitted August 8, 1960

Condensation of salicylaldehyde with ketones is one of the commonest methods of synthesis of benzopyrilium salts. Condensation in presence of alkaline reagents leads to formation as intermediate products of α - β -unsaturated ketones which on treatment with acids undergo cyclization to benzopyrilium salts. The reaction gives unequivocal results, especially when the initial ketone contains only one methylene group. [1].

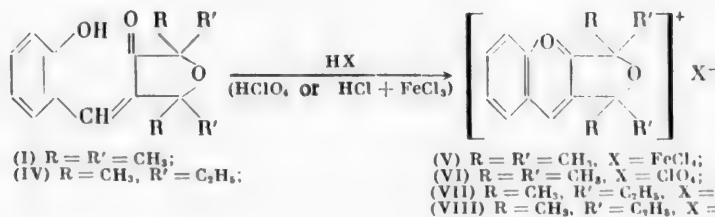
The 2,2,5,5-tetraalkyl-3-furanidones studied by us contain only one methylene group and react with facility with aromatic aldehydes [2]. They were therefore of interest for the synthesis of benzopyrilium salts containing the furanidine ring, in particular since the structure of the resulting salts could be previously assigned unequivocally.

We established that reaction of 2,2,5,5-tetramethyl- and 2,5-dimethyl-2,5-diethyl-3-furanidones with salicylaldehyde in presence of potassium hydroxide gave the corresponding α , β -unsaturated ketones - 4-(α -hydroxybenzylidene)-2,2,5,5-tetramethyl-3-furanidone (I) and 4-(α -hydroxybenzylidene)-2,5-dimethyl-2,5-diethyl-3-furanidone (IV) - whose structure was confirmed by the similarity between their infrared spectra and the infrared spectrum of 4-benzylidene-2,2,5,5-tetramethyl-3-furanidone; the following characteristic bands were reported for the latter: 1730 cm^{-1} (C=O) and 1630 cm^{-1} (C=C) [3].

The structure of the α , β -unsaturated ketone (I) was additionally confirmed by hydrogenation to 4-(α -hydroxybenzyl)-2,2,5,5-tetramethyl-3-furanidone (II) and by methylation with dimethyl sulfate to give 4-(α -methoxybenzylidene)-2,2,5,5-tetramethyl-3-furanidone (III); compound (III) was identical with the 4-(α -methoxybenzylidene)-2,2,5,5-tetramethyl-3-furanidone prepared from α -methoxybenzaldehyde and 2,2,5,5-tetramethyl-3-furanidone.

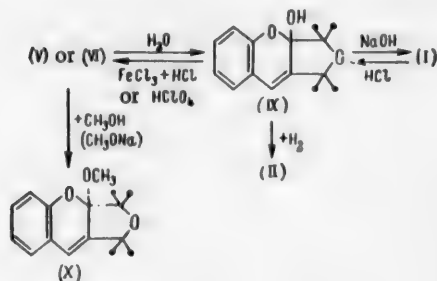


Reaction of the α , β -unsaturated ketones (I & IV) with hydrochloric acid and ferric chloride or perchloric acid leads to formation of 2,3-(2',2',5',5'-tetraalkylfuranidino)-benzopyrilium salts. In the majority of cases we obtained the corresponding furanidinobenzopyrilium ferrichlorides (V & VII) and perchlorates (VI & VIII) in good yields.



We may point out that, unlike the majority of benzopyrilium salts which are deeply colored, the 2,3-(2',2',5',5'-tetraalkylfuranidino)-benzopyrilium perchlorates (VI & VIII) that we prepared are colorless compounds. The ultraviolet spectra of furanidinobenzopyrilium salts possess maxima of absorption bands which are characteristic of this class of compounds [4].

Hydrolysis of salts (V & VI) at room temperature leads to 2,3-(2',2',5',5'-tetramethylfuranidino)-2-chromenol (IX) which is stable only in a neutral medium; under the action of concentrated hydrochloric acid and ferric chloride it regenerates the original furanidinobenzopyrilium salt (V), while with 2 N sodium hydroxide solution the ring opens and the α, β -unsaturated ketone (I) is formed.



The furanidinochromenol (IX) is formed again when hydrogen chloride is passed into an ethereal solution of (I). Hydrogenation of furanidinochromenol (IX) is likewise accompanied by ring opening and leads to 4-(o-hydroxybenzyl)-2,2,5,5-tetramethyl-3-furanidone (II).

The methyl ethers of 2-chromenols can be obtained both from the 2-chromenols themselves [5] and from their benzopyrilium salts [6]. The methyl ether of 2,3-(2',2',5',5'-tetramethylfuranidino)-2-chromenol (X) is smoothly formed on treatment of furanidinobenzopyrilium (V) ferrichloride with methyl alcohol in presence of a small quantity of sodium methoxide.

It has consequently been established that 2,2,5,5-tetraalkyl-3-furanidones are convenient starting substances for the synthesis of furanidinobenzopyrilium salts (V-VIII). It was found possible to isolate both the intermediately formed α, β -unsaturated ketones (I & IV) and the product of hydrolysis of the furanidinobenzopyrilium salts - the furanidinochromenol (IX).

EXPERIMENTAL

4-(o-Hydroxybenzylidene)-2,2,5,5-tetramethyl-3-furanidone (I). To 7.1 g of 2,2,5,5-tetramethyl-3-furanidone and 6.1 g of salicylaldehyde in 30 ml of anhydrous alcohol was added 10 g of potassium hydroxide, and the mixture was heated until it turned dark-red (3 hr). It was then diluted with 100 ml of water and hydrochloric acid was added to give a weakly acidic reaction. Compound (I) was obtained in a yield of 9.5 g (77%), m.p. 150-151° (from alcohol).

Found %: C 73.30, 73.24; H 7.50, 7.45. $C_{15}H_{16}O_3$. Calculated %: C 73.15; H 7.37. Infrared spectrum: 1726 cm^{-1} (C=O, conjugated with F); 1620 cm^{-1} (C=C); 3304 cm^{-1} (OH).

4-(o-Hydroxybenzyl)-2,2,5,5-tetramethyl-3-furanidone (II). Hydrogenation of 1 g of compound (I) in 30 ml of anhydrous alcohol was carried out in presence of palladium on barium sulfate with shaking in the cold. After the calculated amount of hydrogen had been absorbed, the catalyst was separated and the alcohol distilled off. The residue crystallized after prolonged standing. Yield 0.95 g (95%) m.p. 87-89° (from methanol).

Found %: C 72.17, 72.23; H 8.29, 8.09. $C_{15}H_{20}O_3$. Calculated %: C 72.55; H 8.12. Infrared spectrum: 1754 cm^{-1} (C=O of five-membered cyclic ketone); 3484 cm^{-1} (OH).

4-(o-Methoxybenzylidene)-2,2,5,5-tetramethyl-3-furanidone (III). To 6.8 g of o-methoxybenzaldehyde and 7.1 g of 2,2,5,5-tetramethyl-3-furanidone in 10 ml of alcohol was added 10 g of 50% potassium hydroxide solution. Compound (III) came out of solution on the following day. Yield 12.8 g (98%); m.p. 92-93° (from aqueous alcohol).

Found %: C 73.63, 73.50; H 7.94, 7.90. $C_{16}H_{20}O_3$. Calculated %: C 73.82; H 7.74.

b) Into a solution of 1.3 g of (I) in 30 ml of 2 N sodium hydroxide, heated to 30-40°, was stirred 5 ml of dimethyl sulfate. Stirring of the heated mixture was continued for 3 hr. Yield of (III) 0.9 g (65.5%); m.p. 91-93°. No melting point depression in admixture with (III) from the preceding experiment.

4-(*o*-Hydroxybenzylidene)-2,5-dimethyl-2,5-diethyl-3-furanidone (IV). Prepared similarly to (I) from 8.5 g of 2,5-dimethyl-2,5-diethyl-3-furanidone and 6.1 g of *o*-hydroxybenzaldehyde. Yield of (IV) 2 g (14.5%); m.p. 126-127° (from alcohol).

Found %: C 74.36, 74.51; H 7.95, 8.15. $C_{17}H_{22}O_3$. Calculated %: C 74.42; H 8.08. Infrared spectrum: 1726 cm^{-1} (C=O) conjugated with F); 1626 cm^{-1} (C=C); 3268 cm^{-1} (OH).

2,3-(2',2',5',5'-tetramethylfuranidino)-benzopyrilium ferrichloride (V). To 1 g of compound (I) in 10 ml of glacial acetic acid was added a solution of 2 g of ferric chloride in 6 ml of concentrated hydrochloric acid. Ferrichloride (V) came down as bright-yellow crystals. Yield 1.37 g (80%). M.p. 152-153° (from glacial acetic acid).

Found %: C 42.00, 42.00; H 4.14, 4.10; Fe 13.32, 12.98. $C_{15}H_{17}O_2Cl_4Fe$. Calculated %: C 42.19; H 4.01; Fe 13.08. Ultraviolet spectrum: λ_{max} 257, lg ϵ_{max} 4.30; λ_{max} 307, lg ϵ_{max} 3.99; λ_{max} 360, lg ϵ_{max} 3.88 (in glacial acetic acid). Infrared spectrum: 1616 cm^{-1} (C=C, conjugated with the benzene ring).

2,3-(2',2',5',5'-Tetramethylfuranidino)-benzopyrilium perchlorate (VI). To 1 g of (I) in 10 ml of glacial acetic acid was added 2 ml of perchloric acid in 5 ml of acetic anhydride. There was obtained 0.8 g (61.5%) of perchlorate (VI); colorless crystals, m.p. 214-215.5° (with decomp., from glacial acetic acid).

Found %: C 54.77, 54.64; H 5.40, 5.22. $C_{15}H_{17}O_6Cl$. Calculated %: C 54.80; H 5.21. Ultraviolet spectrum: λ_{max} 257, lg ϵ_{max} 4.13; λ_{max} 297, lg ϵ_{max} 3.72; λ_{max} 360, lg ϵ_{max} 3.18 (in glacial acetic acid). Infrared spectrum: 1616 cm^{-1} (C=C, conjugated with the benzene ring).

2,3-(2',5'-dimethyl-2',5'-diethylfuranidino)-benzopyrilium ferrichloride (VII). Prepared similarly to (V) from unsaturated ketone (IV) and a hydrochloric acid solution of ferric chloride. Yield of ferrichloride (VII) 75.5%; bright-yellow crystals, m.p. 89-90° (from glacial acetic acid).

Found %: C 45.16, 45.24; H 4.75, 4.83. $C_{17}H_{21}O_2Cl_4Fe$. Calculated %: C 44.87; H 4.66. Ultraviolet spectrum: λ_{max} 257, lg ϵ_{max} 4.26; λ_{max} 305, lg ϵ_{max} 3.92; λ_{max} 360, lg ϵ_{max} 3.84 (in glacial acetic acid). Infrared spectrum: 1618 cm^{-1} (C=C, conjugated with the benzene ring).

2,3-(2',5'-Dimethyl-2',5'-diethylfuranidino)-benzopyrilium perchlorate (VIII). Prepared similarly to (VI) from unsaturated ketone (IV) and perchloric acid. Yield of perchlorate (VIII) 31%; colorless crystals with m.p. 160-161° (from a mixture of acetic acid and absolute ether).

Found %: C 56.83, 56.84; H 5.88, 5.95. $C_{17}H_{21}O_6Cl$. Calculated %: C 57.22; H 5.93. Ultraviolet spectrum: λ_{max} 260, lg ϵ_{max} 4.21; λ_{max} 297, lg ϵ_{max} 3.60.

2,3-(2',2',5',5'-Tetramethylfuranidino)-2-chromenol (IX). a) To the furanidinobenzopyrilium ferrichloride (V) at room temperature was added water until no more white precipitate appeared. Yield of (IX) quantitative; m.p. 113-114° (from alcohol).

Found %: C 73.16, 73.25; H 7.24, 7.10 $C_{15}H_{18}O_3$. Calculated %: C 73.15; H 7.37.

b) Furanidinobenzopyrilium perchlorate (VI) was washed with water until the wash water gave a neutral reaction. Yield of (IX) quantitative; m.p. 113-114° (from alcohol).

c) A stream of hydrogen chloride was passed into a solution of 1 g of compound (I) in 30 ml of absolute ether for an hour, and the mixture was left overnight. The ether was evaporated and the residue crystallized from alcohol. Yield of furanidinochromenol (IX) quantitative; m.p. 113-114°. A mixed melting test with the preparation from the preceding experiments did not give a depression.

Reactions of 2,3-(2',2',5',5'-Tetramethylfuranidino)-2-chromenol (IX)

2,3-(2',2',5',5'-Tetramethylfuranidino)-benzopyrilium ferrichloride (V). To 1 g of furanidinochromenol (IX) in 10 ml of glacial acetic acid was added 2 g of ferric chloride in 6 ml of concentrated hydrochloric acid. Yield of ferrichloride (V) quantitative; m.p. 152-153° (from glacial acetic acid). No depression of melting point in a mixture with the ferrichloride previously obtained.

4-(Q-Hydroxybenzylidene)-2,2,5,5-tetramethyl-3-furanidone (I). Furanidinochromenol (IX) was gradually dissolved in 2 N sodium hydroxide solution, and the solution neutralized with dilute hydrochloric acid. The precipitated substance was crystallized from alcohol; m.p. 150-151°. No depression of melting point in admixture with (I) previously obtained.

4-(Q-Hydroxybenzyl)-2,2,5,5-tetramethyl-3-furanidone (II). Hydrogenation of 0.85 g of furanidinochromenol (IX) in 30 ml of anhydrous alcohol was effected in the cold in presence of palladium on barium sulfate with shaking. After the calculated quantity of hydrogen had been absorbed, the catalyst was separated and the alcohol distilled. The residue crystallized after lengthy standing. Yield of (II) 0.76 g (88%), m.p. 87-88° (from methanol). No depression of melting point occurred in a mixed test with the (II) obtained by hydrogenation of unsaturated ketone (I).

Methyl ether of 2,3-(2',2',5',5')-tetramethylfuranidino-2-chromenol (X). To a solution of sodium methoxide (from 0.1 g of sodium in 20 ml of anhydrous methanol) was added 0.5 g of furanidinobenzopyrillium ferrichloride (v). Addition of 50 ml of water then brought down the crystalline methyl ether of furanidino-2-chromenol (X). Yield 0.35 g (88.5%), m.p. 93-94° (from methanol).

Found %: C 73.70, 73.86; H 7.91, 7.77. $C_{18}H_{20}O_3$. Calculated %: C 73.82; H 7.74.

A depression of melting point occurred in a mixed test with compound (III) (m.p. 70-75°).

SUMMARY

1. 2,2,5,5-Tetraalkyl-3-furanidones react with salicylaldehyde to give the corresponding α, β -unsaturated ketones, the cyclization of which leads to furanidinobenzopyrillium salts.

2. Hydrolysis of the furanidinobenzopyrillium salts gives furanidinochromenols which are stable only in a neutral medium.

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INVESTIGATIONS ON CONJUGATED SYSTEMS CXLI. ADDITION OF HYDROGEN BROMIDE TO BUTYNONE AND VINYLACETYLENIC KETONES*

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The direction of addition of bromine and hydrogen bromide to enynic hydrocarbons varies according to their structure [1]. Enynic ketones do not add bromine very selectively either at the double or the triple bond, and a nucleophilic mechanism is evidently involved [2]. It was to be expected that the less electrophilic hydrogen bromide would add on more selectively, especially if the mechanism was a nucleophilic one.

With the aim of checking this hypothesis, we investigated the addition of hydrogen bromide to two enynic ketones of different structures - 1-hexen-3-yn-5-one (I) and 3-hexen-1-yn-5-one (II). Addition of hydrogen bromide to the simplest acetylenic ketone - butynone - was also studied for the purpose of comparison.



Vinylacetylenic ketones of both types (I) and (II) easily take up hydrogen bromide from its concentrated aqueous solutions at the ordinary temperature. The addition products are viscous, caustic liquids with the composition $\text{C}_6\text{H}_7\text{OBr}$. They form crystalline derivatives with 2,4-dinitrophenylhydrazine. They polymerize when stored and distilled. The yield of pure products, especially in the case of ketone (I), was therefore extremely low.

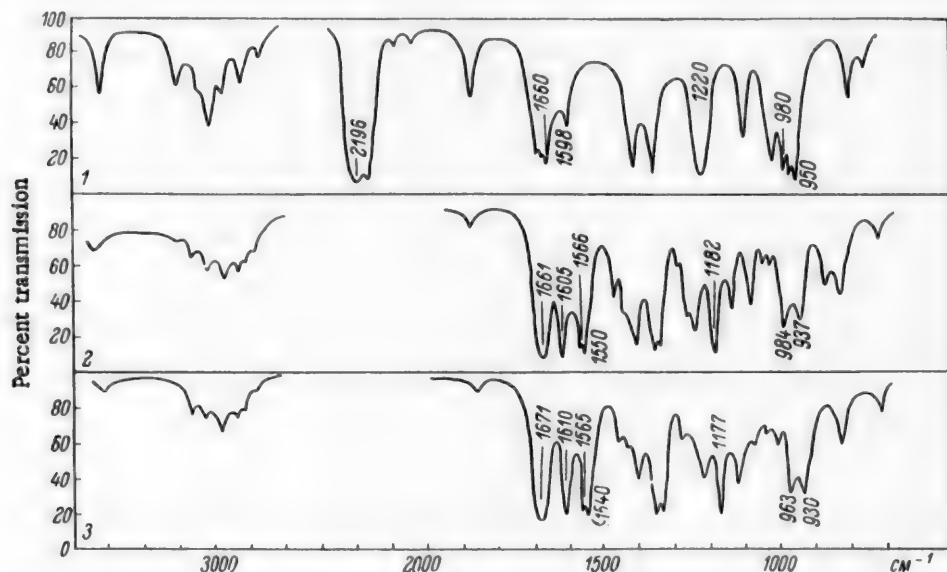


Fig. 1. Infrared transmission spectra. 1) 1-hexen-3-yn-5-one; 2) its hydrobromide prepared by method a; 3) the same hydrobromide prepared by method b.

*Enynic compounds. LVI.

The structure of the bromoketones prepared was verified by the infrared spectra and by chemical methods.

The infrared spectrum of the adduct of hydrogen bromide and ketone (I) (Fig. 1, curve 2) identifies the substance as a dienic bromoketone. The infrared spectrum of the initial ketone (Fig. 1, curve 1) contains strong bands associated with the valence vibrations of the triple (2196 cm^{-1}) and double (1598 cm^{-1}) bonds. Hydrobromination of ketone (I) leads to complete disappearance of the first band, while several bands appear ($1550, 1566, 1605\text{ cm}^{-1}$) in the region of double-bond frequencies which correspond to a conjugated dienic system substituted by bromine. Frequencies characteristic of the vinyl group, in the $900\text{--}1000\text{ cm}^{-1}$ region are present both in the spectrum of the initial ketone and in the spectrum of the hydrobromide.

It is difficult on the basis of the spectral data to decide on the location of the bromine atom, i.e., to choose between formulas (Ia) and (Ib) for the hydrobromide. We consider that formula (Ia) is valid because it was shown in other cases that the bromine atom joins on to the carbon atom most remote from the carbonyl group.



The infrared spectrum of the hydrobromide of ketone (II) likewise reveals its dienic structure. The strong bands of the terminal acetylenic grouping of the initial ketone (2104 and 3284 cm^{-1}) (Fig. 2, curve 1) completely disappear after hydrobromination. In place of one band associated with the double bond in the initial ketone (1598 cm^{-1}), the spectrum of the hydrobromide contains two bands at 1573 and 1602 cm^{-1} which can be associated only with the substituted bromine of the 1,3-dienic system. The strong band in the 970 cm^{-1} region, demonstrating the presence of a --CH=CH-- grouping, is present both in the initial ketone (II) and in its hydrobromide.

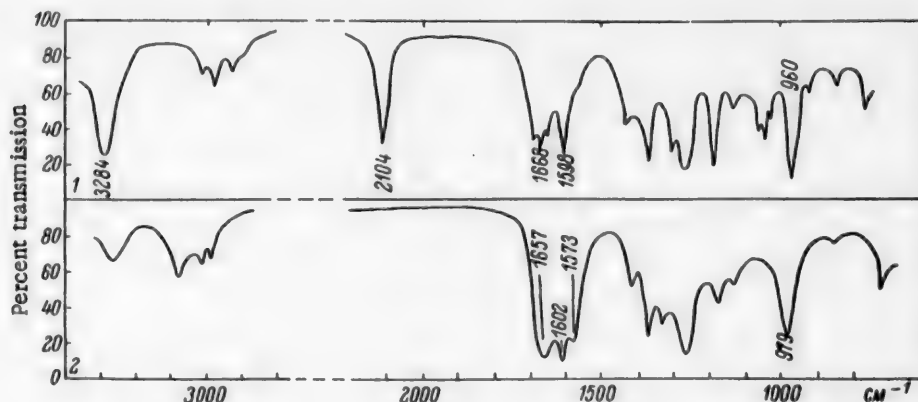


Fig. 2. Infrared transmission spectra. 1) 3-hexen-1-yn-5-one; 2) its hydrobromide.

There was consequently no further doubt that addition of hydrogen bromide to ketone (II) takes place only at the triple bond.

The infrared spectrum of the hydrobromide in this case enables us to choose between the two possible formulas for the 1,3-dienic bromoketone.



Bromoketone (IIb) has a terminal =CH_2 grouping which is characterized by fairly strong absorption in the 890 cm^{-1} region. The hydrobromide of ketone (II) actually obtained does not absorb in this region and at the same time possesses a very broad and strong band at 979 cm^{-1} evidently due to superposition of the absorption bands of the two --CH=CH-- groups. The spectral data consequently confirm formula (IIa) and enable formula (IIb) to be rejected.

Formula (IIa) is also supported by data for the ozonization of the hydrobromide. Attachment of bromine in the 2 position should result in formaldehyde being present in the ozonolysis products after reductive decomposition of the ozonide. In actuality this was not found.

It should be noted that just as in the case of bromination [2], no products of addition of hydrogen bromide in the 1,4 position were detected: absorption in the 1950 cm^{-1} region was not observed in the infrared spectra of both of the isolated hydrobromides.

Under the same conditions butynone (III) forms with hydrogen bromide a crystalline adduct with the composition $\text{C}_4\text{H}_5\text{OBr}$ (probably a mixture of *cis*- and *trans*-isomers). The substance undoubtedly has the structure of 1-bromo-1-buten-3-one since its infrared spectrum contains an extremely strong band at about 940 cm^{-1} which is associated with the $-\text{CH}=\text{CH}-$ grouping, while there is no absorption in the 890 cm^{-1} region ($\text{CH}_2=\text{group}$). The double bond corresponds to the 1575 cm^{-1} band.

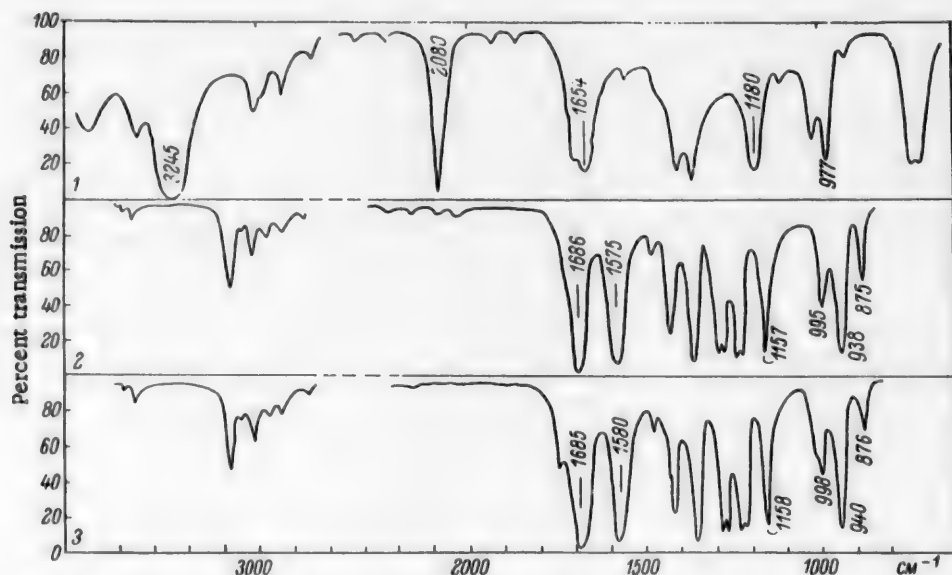


Fig. 3. Infrared transmission spectra. 1) butynone; 2) its hydrobromide obtained by method a; 3) the same hydrobromide obtained by method b.

Formaldehyde was not obtained when the hydrobromide of ketone (III) was subjected to ozone cleavage under the above conditions.

Addition of hydrogen bromide from aqueous solutions to the investigated ketones could proceed both by an electrophilic and a nucleophilic mechanism. In the latter event the position of initial attack is fixed by the bromine atom; in the event of electrophilic addition it must be assumed that ketone (I) adds on hydrogen bromide in the 1,4- and ketone (II) in the 1,6-position with fixation of the hydrogen at the carbonyl group followed by isomerization. For example



Only a nucleophilic mechanism is assigned to reactions of addition of hydrogen halides from solutions of their lithium salts in acetic acid [3,4]. It was of interest to establish whether adducts of the same or different structures are formed by the investigated ketones under conditions ensuring nucleophilic addition.

With this objective we instituted experiments on addition of hydrogen bromide from solutions of lithium bromide in acetic acid to the two ketones (I) and (II).

Under these conditions the crystalline bromoketone formed by butynone is identical with that obtained by addition of hydrogen bromide from aqueous solutions. The identity of the substances was established from the constants and infrared spectrum (Fig. 3, curves 2 and 3).

A similar picture was observed in the case of ketone (I). The infrared spectra of the hydrobromides obtained by the two different routes differed only in the absence of the 863 cm^{-1} frequency and in the differing intensities of the 1073 and 1250 cm^{-1} bands, probably due to the *cis*- and *trans*-forms of the hydrobromide being formed in different ratios, and to the presence of polymeric impurities.

In both cases the reaction proceeded in the initial stage in accordance with a third order equation where $[A]$ is the concentration of the ketone:

$$-\frac{d[Br^-]}{dt} = K_3 [Br^-]^2 [A].$$

A similar reaction – likewise third order – is described in the literature; this order is accounted for by the associated state of the lithium bromide [5].

Replacement of lithium bromide by the chloride leads to a lower velocity constant for the reaction due to the lower nucleophilic activity of the halogen ion.

The velocity of addition of hydrogen bromide to butynone is approximately 56 times greater than that of addition to ketone (I). This may be explained in terms of the change in steric conditions and also of the change in activity of the triple bond. In the case of (I) the triple bond is partly deactivated, as an electrophilic center, by the vinyl group. The occurrence of electronic shifts in these enynic ketones along the conjugated chain was confirmed by measurements of their dipole moments [6].

The present investigation has accordingly established that vinyl-acetylenic ketones, regardless of their structure, add on hydrogen bromide at the triple bond and in the sequence usual for unsaturated carbonyl compounds (contrary to the Markovnikov rule).

EXPERIMENTAL

The methods of preparation of enynic ketones (I) and (II) were described in the preceding communication [2]. Butynone was prepared by oxidation of butynol with chromic mixture. Butynol was prepared in the usual manner from sodium acetylide and acetaldehyde in liquid ammonia. Oxidation of butynol was performed at -10° . Continuous distillation of the butynone was facilitated by application of a vacuum to the reaction vessel and by blowing a strong stream of air through the reaction mixture (a porous glass plate was sealed into the bottom of the cylindrical reaction vessel). The butynone was collected in traps cooled to -60° . The yield was 60%.

B.p. $85-86^\circ$ d_4^{20} 0.8784, n_D^{20} 1.4098, in agreement with literature [7]. Infrared spectrum: \bullet 710 very strong, 733 very strong, 977 very strong, 1018 strong, 1108 weak, 1180 very strong, 1353 very strong, 1402 very strong, 1654 very strong, 1695 very strong, 2080 very strong, 2923 weak, 3008 medium, 3245 very strong cm^{-1} .

Hydrobromination of ketone (I). a) A mixture of 11 g of 1-hexen-3-yn-5-one and 15 g of 41% hydrobromic acid was shaken for an hour at room temperature. Slight heating was observed. The lower layer was collected, washed with water and with sodium bicarbonate solution, dried over CaCl_2 , and distilled in vacuo in a nitrogen atmosphere. There was obtained in this manner 5 g of initial ketone, 1.1 g of hydrobromide (10%), and 10 g of resin.

3-Bromo-1,3-hexadien-5-one. B.p. $50-52^\circ$ (3 mm) d_4^{20} 1.3865, n_D^{20} 1.5399, MR 39.56; calc. 36.75. Found %: Br 45.91. $\text{C}_6\text{H}_7\text{OBr}$. Calculated %: Br 45.67.

2,4-Dinitrophenylhydrazone: Orange needles with m.p. 170° (from a mixture of alcohol and ethyl acetate). Darkens at 140° .

Found %: N 15.25, 15.63; Br 22.49, 22.35. $\text{C}_{12}\text{H}_{11}\text{O}_4\text{N}_4\text{Br}$. Calculated %: N 15.77; Br 22.50

b) A solution of 10.4 g of ketone (I) and 24.7 g of lithium bromide in 50 ml of glacial acetic acid was held at room temperature for five days and then diluted with water. The lower layer was collected and washed with water. The upper layer was extracted with ether. Fractional distillation of the products gave 2 g of bromoketone (Ia) with b.p. $50-52^\circ$ (3 mm), n_D^{20} 1.5370. The infrared spectrum is shown in Fig. 1 (curve 3).

2,4-Dinitrophenylhydrazone: M.p. 170° . A mixture with the preparation obtained from the bromoketone prepared by method a melted at the same temperature.

Kinetic measurements were made by argentometric titration of Br^- and Cl^- ions in samples taken from mixtures of reactants [9]. In all experiments the initial concentration of Br^- and ketones were equal. Results are given in the table.

*Erroneous values were given for the $\text{C}\equiv\text{C}$ and CH_{acet} frequencies in an earlier publication [8].

Rates of Reactions of Unsaturated Ketones with Solutions of Lithium Halides in Acetic Acid ($t^\circ \pm 0.25^\circ$)

Duration (hr)	[Br ⁻] (moles.l. ⁻¹)	K ₁ (moles ⁻² l. ² hr ⁻¹)	Duration (hr)	[Br ⁻] (moles.l. ⁻¹)	K ₂ (moles ⁻² l. ² hr ⁻¹)
1. 1-Hexyn-3-yn-5-one, LiBr, 20°			2. 1-Hexen-3-yn-5-one, LiBr, 50°		
0	1.73	—	0	2.34	—
10	1.44	0.0055	1/2	2.19	0.025
20	1.26	0.0055	1	1.99	0.035
30	1.11	0.0055	2	1.82	0.030
40	1.01	0.0050	3	1.71	0.025
50	0.94	0.0050	4	1.61	0.025
Mean . 0.0053			Mean . . 0.028		
3. 1-Hexen-3-yn-5-one, LiCl, 50°			4. Butynone, LiBr, 50°		
0	2.04	—	0	1.00	—
1	1.88	0.021	1/6	0.81	1.55
2	1.78	0.020	1/3	0.69	1.70
4	1.57	0.021	1/2	0.65	1.40
6	1.43	0.021	Mean . 1.55		
8	1.30	0.022			
10	1.25	0.020			
Mean . 0.021					

Hydrobromination of ketone (II). A mixture of 11 g of 3-hexen-1-yn-5-one and 25.4 g of hydrobromic acid was shaken for 2.5 hr at room temperature (mixing performed with water cooling). The lower layer was then separated, washed with water, and dried over CaCl_2 . Vacuum distillation (in a nitrogen stream) gave 6 g of initial ketone, 2.5 g of hydrobromide (27%), and 2.5 g of residue.

1-Bromo-1,3-hexadien-5-one: b.p. $74-75^\circ$ (4 mm), d_4^{20} 1.4012, n_D^{20} 1.5688, MR 40.91; calc. 36.75. Found %: Br 45.46, 45.61. $\text{C}_6\text{H}_7\text{OBr}$. Calculated %: Br 45.67.

2,4-Dinitrophenylhydrazone: Red needles. M.P. $154-154^\circ$ (from a mixture of alcohol and ethyl acetate).

Found %: N 15.88, 15.65; Br 22.43, 22.67. $\text{C}_{12}\text{H}_{11}\text{N}_4\text{O}_4\text{Br}$. Calculated %: N 15.77; Br 22.50.

A solution of 0.5 g of bromoketone in 30 ml of ethyl chloride, cooled to -40° , was subjected to ozonization for 3 hr. After the solvent had evaporated, the ozonides were decomposed with 20% potassium iodide solution, and the released iodine was reduced with sodium thiosulfate.

The resulting solution did not give a precipitate of dinaphtholmethane on heating with 8-naphthol solution [10]. Qualitative reactions for formic acid and pyruvic acid were positive.

The solid distillation residue contained 12.87% of Br.

Hydrobromination of butynone (III) a A mixture of 5.5 g of butynone and 24 g of 41% hydrobromic acid was shaken at room temperature for 2 hr, after which the resulting crystalline mass (9.5 g, 79%) was separated. After recrystallization from ligroine, the 1-bromo-1-buten-3-one melted at $38-38.5^\circ$. Colorless needles.

Found %: Br 53.66, 54.10. $\text{C}_4\text{H}_5\text{OBr}$. Calculated %: Br 53.63. Infrared spectrum: 875 weak, 938 very strong, 995 medium, 1014 medium, 1157 very strong, 1220 very strong, 1232 very strong, 1272 very strong, 1287 very strong, 1359 very strong, 1424 very strong, 1478 weak, 1575 very strong, 1686 very strong, 2929 very strong, 2972 weak, 3015 weak, 3047 weak, 3077 medium, cm^{-1} .

The substance can be stored for one day, after which it quickly resinifies.

2,4-Dinitrophenylhydrazone: Orange needles, m.p. 196° (from a mixture of alcohol and ethyl acetate). At 150° the color changes to yellow.

Found %: N 17.37, 17.25; Br 24.31, 24.33. $C_{10}H_9O_4N_4Br$. Calculated %: N 17.03; Br 24.29.

Formaldehyde was not found among the cleavage products after ozonization of a weighed sample of the bromoketone under the conditions described earlier.

b) A solution of 3 g of butynone and 3.5 g of lithium bromide in 10 ml of glacial acetic acid was held for three days at room temperature, and then worked up by the procedure described earlier. There was obtained 3.1 g of oil which quickly crystallized. The compound had m.p. 38-38.5° and did not give a depression of melting point in admixture with authentic 1-bromo-1-buten-3-one. The 2,4-dinitrophenylhydrazone melted at 196° and did not give a depression in admixture with the preparation of the same derivative of the bromoketone obtained by method a. The analytical data for the bromoketone and the 2,4-dinitrophenylhydrazone were also satisfactory.

Kinetic measurements were carried out under the conditions described earlier.

The infrared spectra were plotted with the IKS-14 spectrophotometer (LiF and NaCl prisms) with a layer thickness for the solutions of 0.25 mm, and for the pure substances of 0.01 mm.

SUMMARY

1. The direction of addition of hydrogen bromide to butynone, 1-hexen-3-yn-5-one, and 3-hexen-1-yn-5-one was studied. It was shown that addition proceeds at the triple bond with formation, respectively, of 1-bromo-1-buten-3-one, 3-bromo-1,3-hexadien-5-one, and 1-bromo-1,3-hexadien-5-one.

2. It was established that addition proceeds in the same direction when two of these ketones are treated with solutions of lithium bromide in acetic acid.

3. Exploratory experiments showed that in the latter case the reaction is of the third order, and butynone reacts approximately 56 times faster than 1-hexen-3-yn-5-one.

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STUDIES OF CONJUGATED SYSTEMS

CXLII. THE ADDITION OF TRIPHENYLMETHYL RADICALS TO VINYLACETYLENE AND ITS HOMOLOGS*

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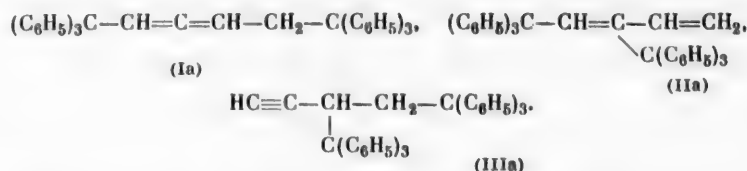
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Among the numerous addition reactions of enyne hydrocarbons, very few can with certainty be assigned to radical processes [1]. It is possible to carry out the chloroarylation of enynes, according to a radical mechanism, with the aid of diazo compounds which was studied recently by A. V. Dombrovskii [2] and the authors of the present paper [3]. Only one example of the direct addition of stable free radicals has been described: triphenyl methyl was added to isopropenylacetylene in the 1,4 position [4]. In the meantime a study of the influence of the structure of the enynes on the order of addition of free radicals has been of undoubted interest, since it is possible to favor the appearance of the addition mechanism in other reactions. Moreover, crystalline addition products may be convenient for the identification of the original hydrocarbons.

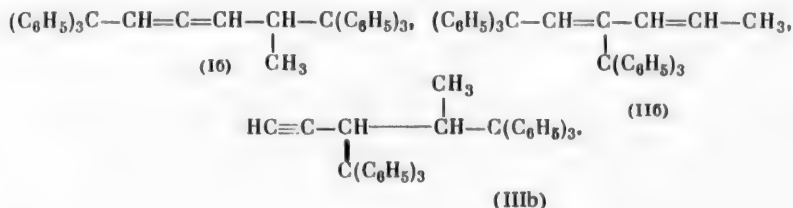
With these considerations in mind, we have carried out systematic studies in our laboratory on the chemistry of enynes in their reactions with free radicals. This paper describes the results of our experiments on the addition of triphenylmethyl radicals to enyne hydrocarbons of various structures.

By adding triphenylmethyl radicals to vinylacetylene one might expect the formation of the following three compounds

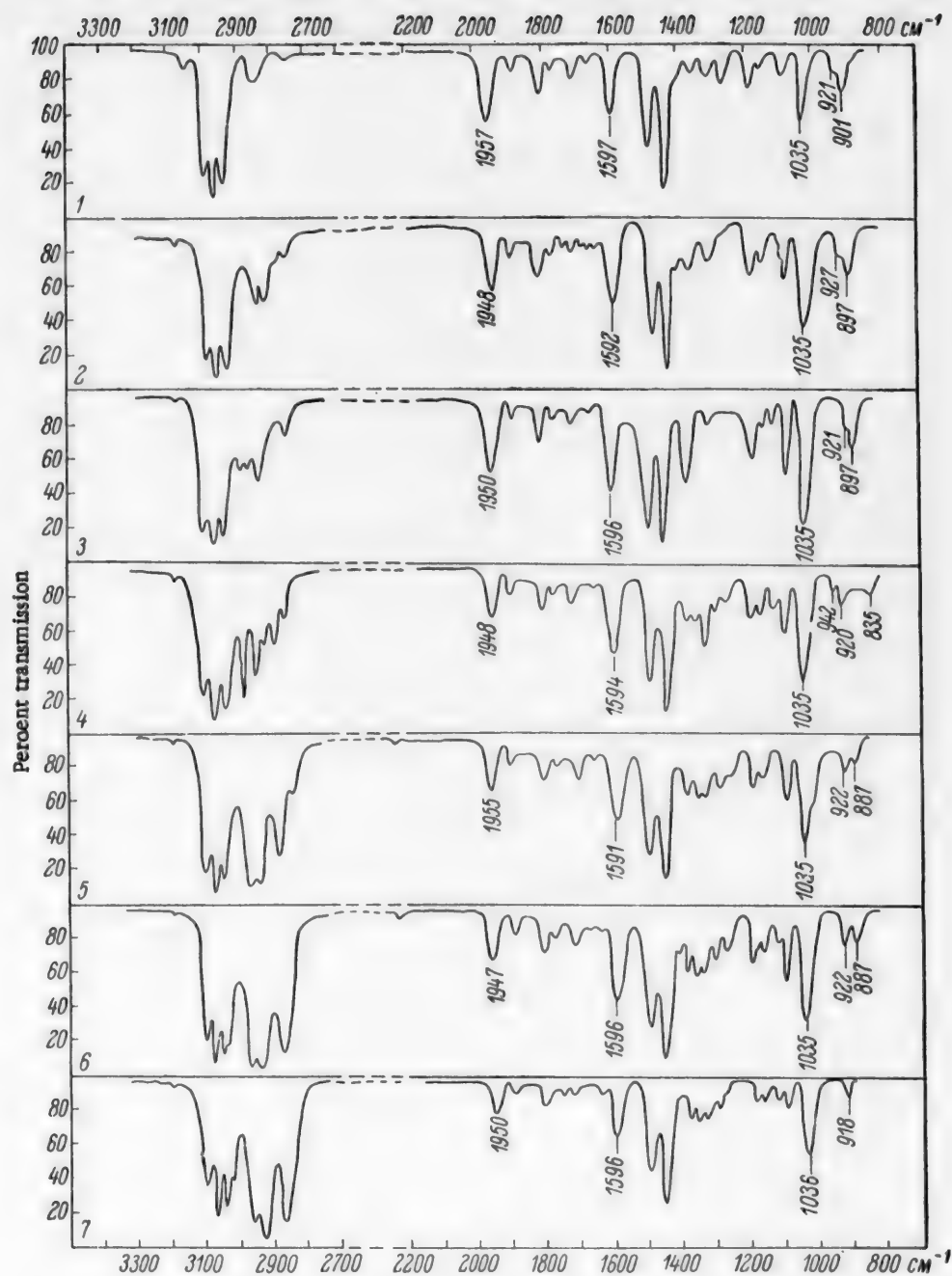


The crystalline addition product that was actually obtained was an allene hydrocarbon (Ia). The frequencies of the vinyl (in the 900-1000 cm^{-1} region) and acetylene (in the 2100 and 3300 cm^{-1}) groups were observed in its infrared spectrum (Curve 1) and there was a fairly intensive band of vibrations of the allene system (about 1950 cm^{-1}).

Analogous results were also obtained in the case of propenylacetylene. The crystalline addition product showed a band of valence vibrations of the allene group while the valence or deformation vibrations of the end acetylene group and the $-\text{CH}=\text{CH}-$ group (about 950 cm^{-1}), which should be found in the spectra of the possible addition products (IIb) and (IIIb) (Curve 2), were absent.

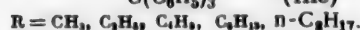


* Enyne Compounds. LVII



Infrared transmission spectra (3% solutions in CCl_4 , layer thickness $1000\ \mu$). 1) 1,1,1,6,6,6-hexaphenylhexadiene-2,3; 2) 5-methyl-1,1,1,6,6,6-hexaphenylhexadiene-2,3; 3) 2-methyl-1,1,1,6,6,6-hexaphenylhexadiene-2,3; 4) 2-ethyl-1,1,1,6,6,6-hexaphenylhexadiene-2,4; 5) 2-butyl-1,1,1,6,6,6-hexaphenylhexadiene-2,3; 6) 2-hexyl-1,1,1,6,6,6-hexaphenylhexadiene-2,3; 7) 2-octyl-1,1,1,6,6,6-hexaphenylhexadiene-2,3.

In the case of vinylmethylacetylene, and also vinylethyl-, vinylbutyl-, vinylhexyl- and vinyloctylacetylenes the crystalline addition products were also allene hydrocarbons of type (Ic). They did not contain admixtures of isomers of type (IIc) since their spectra did not show the frequencies of the vinyl group, but they possibly contained a very slight admixture of addition products with an acetylene bond (IIIc); a very weak absorption was observed in their spectra at about $2240\ \text{cm}^{-1}$ where compounds with a triple bond usually absorb:



2388

Found, %: C 93.08, 92.92; H 6.81, 6.93. $C_{22}H_{18}$. Calculated %: C 92.99; H 7.01

SUMMARY

1. A series of addition reactions of triphenylmethyl radicals to vinyl-, propenyl-, vinylmethyl-, vinylethyl-, vinylbutyl-, vinylhexyl- and vinyloctylacetylenes was studied.

2. It was shown that in all cases 1,4 addition of the free radicals occurs with the formation of the corresponding allene hydrocarbons.

3. With increasing molecular weight of the alkyls the melting point of the addition products decreases, however, right up to vinyloctylacetylene; the crystalline products obtained can be used for the identification of the original enyne hydrocarbons.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

SOME PROPERTIES OF ENOL ACETATES

VII. THE ENOL ACETATE OF CYCLOBUTANONE AND ITS CONVERSION α -ALKYLCYCLOBUTANONES

I. V. Machinskaya, G. P. Smirnova and V. A. Barkhash

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 8,
pp. 2563-2566, August 1961

Original article submitted September 12, 1960

We have shown in previous papers [1-3] that enol acetates of aldehydes and ketones are substances from which various organic compounds can be synthesized. Among others, the enol acetate of cyclohexanone was used for these syntheses. It seemed worthwhile to investigate how the reaction which we previously studied would proceed with the enol acetates of cyclanones with a different number of members in the ring, which might permit finding some regularities in the dependence of the properties of the cyclanones on the size of the ring. In the present study we worked out a method of preparing the enol acetate of cyclobutanone which was not previously known, and studied its bromination by N-bromosuccinimide and the reaction of the resulting bromine derivative with ethyl magnesium bromide.

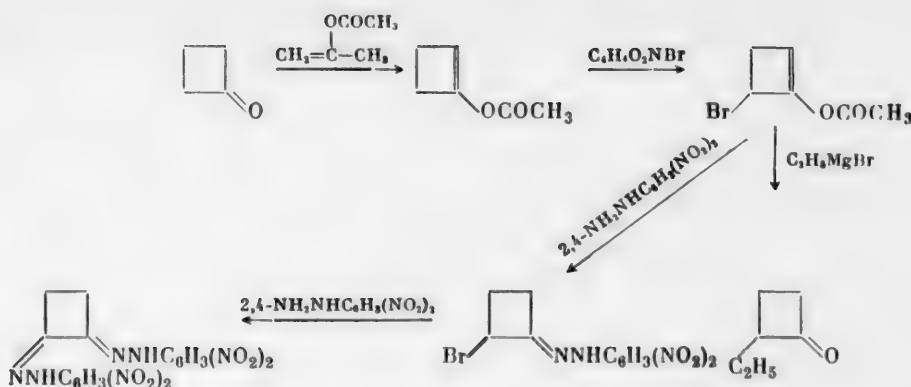
The formation of the enol acetate of cyclobutanone requires the introduction of a double bond into a four-membered ring, which causes difficulty in preparing this compound; therefore we made use of a more energetic enolacetylating reagent - isopropenylacetate in the presence of acetylsulfoacetic acid ($\text{CH}_3\text{COOSO}_2\text{-CH}_2\text{COOH}$). The reaction was carried out with heating and with continuous distillation of acetone. The structure was confirmed by the analytical data, and also by the infrared spectrum.

Bromination of the enol acetate of cyclobutanone by N-bromosuccinimide under the conditions we described previously [4], led to the formation of 3-bromo-2-acetoxycyclobutene-1. By reacting this with the aqueous methanol solution of 2,4-dinitrophenylhydrazine sulfate at room temperature, the 2,4-dinitrophenylhydrazone of α -bromocyclobutanone was obtained; it is apparent that from the beginning of this reaction, saponification of the enol acetate group occurs due to the influence of sulfuric acid with the formation of bromoketone. The hydrazone obtained on heating with an excess of 2,4-dinitrophenylhydrazine, gives bis (2,4-dinitrophenylhydrazone) cyclobutanedione-1,2. Both these compounds were prepared previously [5,6]. These reactions show without doubt that on brominating the enol acetate of cyclobutanone by means of N-bromosuccinimide, a bromine atom enters into the α -position relative to the acetoxy group as also occurs on brominating the enol acetate of cyclohexanone [4]. In connection with the preparation of the stable 3-bromo-2-acetoxycyclobutene-1, it should be noted that several investigators [7,8] tried unsuccessfully to achieve the allyl bromination of cyclobutene by means of N-bromosuccinimide. Apparently the acetoxy group at the double bond has a stabilizing effect on the cyclobutene ring.

We also studied the reaction of 3-bromo-2-acetoxycyclobutene-1 with ethyl magnesium bromide for the purpose of preparing α -ethylcyclobutanone. It should be noted that only α -methylcyclobutanone is described in the literature; however it was not separated in the free form [9]. Attempts to prepare alkylcyclobutanones by the reaction of ketene with diazoalkanes did not give positive results; on acidifying alkylmethylenecyclobutanes, isomeric alkylcyclopentanones [10] were formed instead of the expected alkylcyclobutanones. By reacting 3-bromo-2-acetoxycyclobutene-1 with two moles of ethyl magnesium bromide, we obtained α -ethylcyclobutanone.

Thus, the reaction of bromine-substituted enol acetates of cyclobutanone with ethyl magnesium bromide proceeds analogously to those of other bromine-substituted enol acetates that we studied previously: along with the substitution of a bromine atom by an alkyl group the enol acetate group splits off and the carbonyl group is regenerated. The method which has been worked out for the alkylation of cyclobutanone through bromine-substituted enol acetate opens up a way to prepare various α -alkylcyclobutanones.

The reactions which we carried out may be shown as follows:



The original cyclobutanone was prepared by the reaction of ketene with diazomethane. There was only very scanty information about this reaction in the literature [11-13] and therefore the method had to be specially worked out. We prepared isopropenyl acetate by the reaction of ketene with acetone in the presence of acetylsulfoacetic acid.

EXPERIMENTAL

Cyclobutanone. An ether solution of diazomethane, prepared from 158 g of nitrosomethyl carbamide in 600 ml of ether and 480 ml of a 40% aqueous solution of caustic potash, was placed in a flask equipped with a tube reaching nearly to the bottom for the introduction of ketene and a reflux condenser. The mixture was cooled with a mixture of dry ice and acetone and the ketene passed in after having been passed through a trap cooled by the same mixture in order to collect the entrained acetone. The reaction ceased in about 1.5 hours with a productivity of the ketene lamp of ~ 14 g of ketene per hour. After removing the cooling mixture, nitrogen was passed through the solution until the mixture reached room temperature; then it was dried over anhydrous sodium sulfate, the ether distilled off and the remaining material distilled. 38.7 g of cyclobutanone (36.1% calculated on the amount of nitrosomethyl carbamide) was obtained.

B.p. $98-99^\circ$; n_D^{20} 1.4184, d_4^{20} 0.9322, M_R 18.96; calc. 18.94. Ketone content 99.4% (by formation of oxime). Infrared spectrum (cm^{-1}): 842, 966, 1011, 1090, 1214, 1251, 1401, 1791, 2130, 2973, 3005, 3560. For data in the literature see [15].

The enol acetate of cyclobutanone. A mixture of 50 g of cyclobutanone, 142 g of isopropenylacetate (b.p. $94-96^\circ$; n_D^{20} 1.3985, d_4^{20} 0.9188), 6 g of acetylsulfoacetic acid* and 0.4 g of copper acetate were heated at $110-120^\circ$ while slowly distilling acetone through the column. The distillation was continued for five hours and each hour a quantity of isopropenyl acetate was added equivalent to the acetone distilled off (altogether 50 ml of acetone was distilled). The mixture was cooled, and then shaken with 17 g of NaHCO_3 in 80 ml of water; the organic layer was separated and the aqueous layer repeatedly extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether distilled off. By fractionating the residue *in vacuo* 32.6 g (40.8%) of the enol acetate of cyclobutanone was obtained.

B.p. $45.5-47^\circ$ (25 mm) n_D^{20} 1.4113, d_4^{20} 0.9598, M_R 29.03; calc. 29.25. Found %: C 64.12, 64.15; H 7.24, 7.31. Saponification number 495.6. $\text{C}_6\text{H}_8\text{O}$. Calculated %: C 64.27; H 7.19. Saponification number 499.5. Infrared spectrum (cm^{-1}): 600, 633, 900, 971, 1005, 1050, 1085 ($-\text{C}=\text{C}-\text{O}-\text{C}$), 1133, 1217, ($-\text{C}=\text{C}-\text{O}-\text{C}$), 1300, 1381, 1400, 1652 ($\text{C}=\text{C}$), 1728, 1770 ($\text{C}=\text{O}$), 1839, 2938, 2974 ($=\text{CH}$).

3-Bromo-2-acetoxycyclobutene-1. A mixture of 19 g of N-bromosuccinimide, 12 g of the enol acetate of cyclobutanone and 21 ml of anhydrous carbon tetrachloride was heated in a flask with a reflux condenser on a water bath up to 60° ; when a vigorous reaction began, heating was discontinued. When the boiling was over, the reaction mixture was cooled, the succinimide removed, the precipitate washed with CCl_4 and the filtrate washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off *in vacuo*. By fractionating the remaining material 7.6 g (37.2%) of 3-bromo-2-acetoxycyclobutene-1 was obtained.

* A mixture of 144 g of acetic anhydride and 40 ml of concentrated sulfuric acid was heated for 30 minutes at 80° . The acetic acid was distilled off *in vacuo*; the dark, viscous residue was used as a catalyst.

B.P. 44-45.5° (4 mm) n_D^{20} 1.4353, d_4^{20} 1.3152, MR_D 37.91; calc. 37.96. Found %: C 37.86, 37.63; H 3.68, 3.78; Br 41.84, 41.99. The saponification number was 589.7. $C_8H_7O_2Br$. Calculated %: C 37.73; H 3.69; Br 41.84. Saponification number 596.48*.

2,4-Dinitrophenylhydrazone of α -bromocyclobutanone from 3-bromo-2-acetoxycyclobutene-1. A mixture of 20 ml of CH_3OH and 6 ml of water was added to a solution of 1.34 g of 2,4-dinitrophenylhydrazine in 3 ml of concentrated sulfuric acid and then 1.3 g of 3-bromo-2-acetoxycyclobutene-1 (molar ratio 1 : 1) was immediately poured in. A dark brown precipitate was formed immediately. It was washed with CH_3OH . M.p. 127-127.5° (from a mixture of $CHCl_3$ and CH_3OH). The literature shows m.p. 127-128° [8].

Found %: C 36.39, 36.41; H 2.79, 2.83; Br 24.17, 24.14; N 17.12, 17.15. $C_{10}H_9O_4N_4Br$. Calculated %: C 36.49; H 2.76; Br 24.28; N 17.02.

Bis (2,4-dinitrophenylhydrazone) cyclobutanedione-1,2. A mixture of 5 ml of CH_3OH and 1.5 ml of water was poured into a solution of 0.33 g of 2,4-dinitrophenylhydrazine in 1 ml of concentrated sulfuric acid and then 0.25 g of the 2,4-dinitrophenylhydrazone of α -bromocyclobutanone (molar ratio 2 : 1) was added. This was boiled for two hours and then cooled. M.p. 280-280.5° (from a mixture of $CHCl_3$ and CH_3OH). The literature shows: m.p. 282-283° [8].

Found %: C 43.41, 43.40; H 2.89, 2.84; N 25.35, 25.31. $C_{16}H_{12}O_8N_8$. Calculated %: C 43.47; H 2.72; N 25.22.

α -Ethylcyclobutanone. Ethyl magnesium bromide (from 5.27 g of Mg and 31.4 g of C_2H_5Br in 250 ml of absolute ether) was added drop by drop with vigorous stirring and cooling with ice to 20.7 g of 3-bromo-2-acetoxycyclobutene-1 in 250 ml of absolute ether. A white precipitate came down immediately; the mixture was stirred for 40 minutes in the cold and for 7.5 hours while heating on a water bath. Decomposition was accomplished by means of a saturated solution of NH_4Cl . After repeated extraction, the ether extracts were dried by means of sodium sulfate, the solvent was distilled off in vacuo and the remaining material was fractionated. 1.9 g (17.9%) of α -ethylcyclobutanone was obtained.

B.p. 72-76° (25 mm) n_D^{20} 1.4592, d_4^{20} 0.9582, MR_D 28.01; calc. 28.13. The ketone content was 99.0% (by the formation of oxime). Found, %: C 73.18, 73.21; H 10.35, 10.29. $C_6H_{10}O$. Calculated %: C 73.42; H 10.27. Infrared spectrum (cm^{-1}): 667, 929, 970, 1027, 1069, 1100, 1138, 1195, 1521, 1392, 1436, 1478, 1640, 1711, 2889, 2945, 2980.

2,4-Dinitrophenylhydrazone, m.p. 159.5-160° (from a mixture of anhydrous alcohol and ethylacetate).

Found %: N 19.98, 19.91 $C_{12}H_{14}O_4N_4$. Calculated %: N 20.14.

SUMMARY

1. The synthesis of the enol acetate of cyclobutanone was accomplished by reacting cyclobutanone with isopropenylacetate in the presence of acetylsulfoacetic acid.

When the enol acetate of cyclobutanone reacts with N-bromosuccinimide, 3-bromo-2-acetoxy-cyclobutane-1 is formed.

3. The reaction of the bromoenolacetate of cyclobutanone with two moles of ethyl magnesium bromide gives α -ethylcyclobutanone. This reaction may serve as a method of preparing α -alkylcyclobutanones.

4. A method for preparing cyclobutanone from diazomethane and ketene was worked out.

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* Calculating on the basis of two equivalents of alkali since dehydrobromination proceeds in this way also.

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THE SYNTHESIS OF COMPOUNDS CONTAINING RESIDUES OF FOLIC ACID

I. THE SYNTHESIS OF SOME DERIVATIVES OF GLUTAMIC ACID

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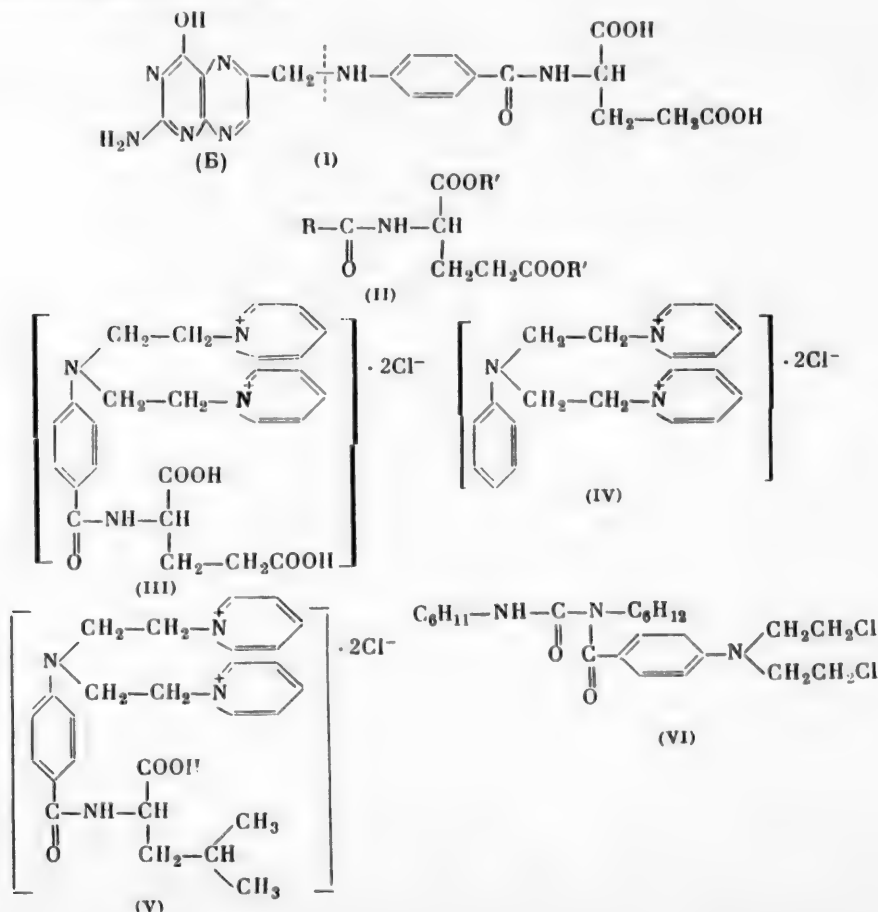
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 8,
pp. 2567-2572, August 1961

Original article submitted August 25, 1960

Among the large number of derivatives and structural analogs of pteroylglutamic (folic) acid (I) there are many which possess physiological activity, including the ability to arrest the growth of cancerous tumors [1-6]. In our opinion substances that are, so to speak, "residues" of a molecule of pteroylglutamic acid are of interest, and among them are compounds containing cytotoxic groups.

This paper describes the synthesis of similar compounds which contain residues of the right half of molecule (I) - (A), namely, of derivatives of glutamic acid with the general formula (II).

p-Nitrobenzoyl-*d*, *l*-glutamic acid (No. 1 in the table) was prepared by condensing *p*-nitrobenzoyl chloride with *l*-glutamic acid according to the Schotten-Baumann reaction. By catalytically reducing *p*-nitrobenzoyl-*d*, *l*-glutamic acid by hydrogen in the presence of a nickel catalyst, *p*-aminobenzoyl-*d*, *l*-glutamic acid is formed and is separated as the chlorohydrate [4] (No. 2).



The diethyl ester of p-aminobenzoyl-d, *l* -glutamic acid (No. 3) was prepared by the esterification of p-aminobenzoyl-d, *l* -glutamic acid by means of anhydrous alcohol saturated with hydrogen chloride; in this way the step of separating and purifying p-aminobenzoyl-d, *l* -glutamic acid was avoided. By condensing salicylic acid with the diethyl ester of *l* -glutamic acid in the presence of 1,3-dicyclohexylcarbodiimide in accordance with Sheehan's method [8], the diethyl ester of o-hydroxybenzoyl-d, *l* -glutamic acid (No. 5) is formed.

The diethyl ester of p-dimethylaminobenzoyl-d, *l* -glutamic acid (No. 6) was synthesized in two ways: first, by the methylation of the diethyl ester of p-aminobenzoyl-d, *l* -glutamic acid by means of methyl iodide in the presence of KOH; second, by the condensing p-dimethylaminobenzoic acid with the diethyl ester of *l* -glutamic acid in the presence of 1,3-dicyclohexylcarbodiimide. The latter method gives a higher yield and a purer product than the first method.

p-Bis(β -chloroethyl)aminobenzoyl-d, *l* -glutamic acid (No. 7) is formed by the reaction of *l* -glutamic acid with the chloride of p-bis(β -chloroethyl)-aminobenzoic acid [9].

In view of the instability of the β -chlorine atoms of the N-mustard group in alkaline solution, the condensation was carried out at a pH of not more than 7.5-8 and a small yield of the condensation product was obtained. In this connection, efforts to synthesize this substance by methods that would exclude water from the reaction mixture (in pyridine; in xylene; with no solvent) were made. However no positive results were obtained. Thus, when the condensation was carried out in pyridine, compound (III) was formed which, in an aqueous solution in the cold, quantitatively precipitates AgCl when a solution of AgNO₃ is added; this indicates the presence of chlorine in the ionic state. The fact that one obtains compounds (IV) and (V) with similar properties serves as indirect confirmation of structure (II).

The diethyl ester of p-bis(β -chloroethyl)aminobenzoyl-d, *l* -glutamic acid (No. 8) was also synthesized by two methods: by the β -hydroxyethylation of the diethyl ester of p-aminobenzoyl-d, *l* -glutamic acid by ethylene oxide with subsequent conversion to the dichlorodiethyl derivative by the action of PCl₅; and by the condensation of the chloride of p-bis(β -chloroethyl)aminobenzoic acid with the diethylester of *l* -glutamic acid in an ether-alcohol solution in the presence of triethylamine as a base.

When p-bis(β -chloroethyl)aminobenzoic acid was condensed with the diethyl ester of *l* -glutamic acid in the presence of 1,3-dicyclohexylcarbodiimide, instead of the expected condensation product (No. 8), a substance was obtained which appeared to be an N-acyl derivative of 1,4-dicyclohexyl carbamide (VI).

EXPERIMENTAL

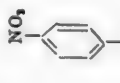
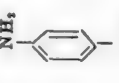
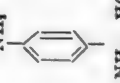
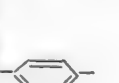
The hydrochloride of p-aminobenzoyl-d, *l* -glutamic acid. 5 g of p-nitrobenzoyl-d, *l* -glutamic acid was dissolved in 75 ml of anhydrous alcohol and a nickel catalyst added; the mixture was agitated while hydrogen was passed through during a five hour period at room temperature. The catalyst was filtered off, the filtrate evaporated to half volume in vacuo, then shaken with activated carbon and filtered. After cooling, the solution was saturated with dry hydrogen chloride after which 400 ml of absolute ether was poured in in portions, with stirring. A white crystalline precipitate (colorless needles) of the hydrochloride of p-aminobenzoyl-d, *l* -glutamic acid was formed (see table, compound 4).

The diethyl ester of p-aminobenzoyl-d, *l* -glutamic acid. 10 g of p-nitrobenzoyl-d, *l* glutamic acid in 150 ml of anhydrous alcohol was shaken for five hours while passing in hydrogen in the presence of a nickel catalyst. The residue was removed and the filtrate saturated with dry hydrogen chloride at 0° and boiled for 3.5 hours. The solution was mixed with activated carbon, filtered and poured into 350 ml of water. A small quantity of by-product in the form of an oil was extracted with ether. The aqueous layer was separated and neutralized by ammonia, with cooling. A precipitate of colorless needles was formed (see table, compound 3).


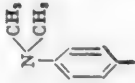
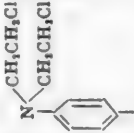
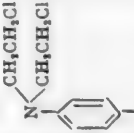
The diethyl ester of o-hydroxybenzoyl-d, *l* -glutamic acid. 2.4 g of the hydrochloride of the diethyl ester of *l* -glutamic acid was dissolved in 5 ml of anhydrous alcohol and then 1 g of triethylamine and 20 ml of absolute ether were added. The hydrochloride of triethylamine, which precipitated on cooling, was filtered off and 1.4 g of salicylic acid and 2 g of 1,3-dicyclohexylcarbodiimide in 4 ml of chloroform were added to the filtrate. The mixture was stirred vigorously and allowed to stand overnight at room temperature. The precipitate was filtered off, the solvent evaporated, and the remaining oil distilled in vacuo B.p. 130-135° (6 mm) (Table, Compound 5).

The diethyl ester of p-dimethylaminobenzoyl-d, *l* -glutamic acid. a) diethyl ester of p-aminobenzoyl-d, *l* -glutamic acid was suspended in 20 ml of methyl alcohol and 2.85 g of methyl iodide and a solution of 570 mg of



No.	R	R'	M.p.	Yield, %	Empirical formula	% C		% H		% N		% Cl	
						found	calc.	found	calc.	found	calc.	found	calc.
1*		H	110—111°	68—70	$\text{C}_{12}\text{H}_{12}\text{O}_7\text{N}_2$	48.48, 48.68	48.65	4.12, 4.10	4.05	9.28, 9.37	9.46	—	—
2*		H	172—173	66—70	$\text{C}_{12}\text{H}_{14}\text{O}_5\text{N}_2$	54.29, 54.08	54.15	5.29, 5.34	5.26	10.64, 10.78	10.53	—	—
3*		C_2H_5	143—144	84—90	$\text{C}_{16}\text{H}_{22}\text{O}_5\text{N}_2$	59.84, 59.69	59.62	6.91, 6.88	6.83	8.80, 8.58	8.69	—	—
4		H	197—198	90—95	$\text{C}_{13}\text{H}_{15}\text{O}_5\text{N}_2\text{Cl}$	47.82, 47.78	47.60	4.98, 4.90	4.96	9.35, 9.43	9.26	11.68, 11.79	11.75

* After completion of the synthesis of compounds 1-3, a paper [7] appeared in the literature describing the synthesis of these compounds with identical constants, but prepared by somewhat different methods.

No.	R	R'	M.p.	Yield, %	Empirical formula	% C		% H		% N		% Cl	
						found	calc.	found	calc.	found	calc.	found	calc.
5		C_2H_5	B.P. 130—135 (6 mm)	70—75	$C_{16}H_{21}O_6N$	59.03, 59.25	59.44	6.52, 6.38	6.50	4.01, 4.18	4.23	—	—
6		C_2H_5	91—92	51—90	$C_{18}H_{26}O_5N_2$	61.80, 61.89	61.71	7.51, 7.48	7.43	8.08, 8.19	8.00	—	—
7		H	156—158	2—3.5	$C_{16}H_{20}O_5N_2Cl_2$	—	—	—	—	6.88, 6.74	7.16	18.38, 17.99	18.15
8		C_2H_5	61—62	67—82	$C_{20}H_{28}O_5N_2Cl_2$	53.68, 53.77	53.69	6.06, 6.23	6.26	6.28, 5.93	6.26	—	—

KOH in 10 ml of methyl alcohol was added. The solution was boiled for three hours and then the solvent was evaporated at room temperature. The remaining material was dissolved by boiling in 25% alcohol, the solution mixed with activated carbon, filtered and cooled. The oil that separated crystallized in the form of colorless needles on prolonged cooling (Table, Compound 6).

b) 2.4 g of the hydrochloride of the diethyl ester of *l*-glutamic acid was dissolved in 5 ml of anhydrous alcohol and 1.3 ml of triethylamine and 20 ml of absolute ether were added. The mixture was cooled by ice and the triethylamine hydrochloride was filtered off. 1.65 g of *p*-dimethylaminobenzoic acid and 2 g of 1,3-dicyclohexylcarbodiimide in 2 ml of chloroform were added. The mixture was shaken and allowed to stand at room temperature overnight. The precipitate of dicyclohexyl carbamide was filtered off and the filtrate evaporated. The material that remained was an oil which crystallized in the form of colorless needles on prolonged standing in the refrigerator.

Condensation of the chloride of *p*-bis(β -chloroethyl)aminobenzoic acid with *l*-glutamic acid. a) 2.9 g of the chloride of *p*-bis(β -chloroethyl)aminobenzoic acid was added, with vigorous stirring, to a solution of 1.47 g of *l*-glutamic acid in 15 ml of a saturated solution of sodium bicarbonate at 40-45°. The reaction mixture was stirred for 1.5 hours at 40°, then cooled and acidified to pH 4 by means of hydrochloric acid. The residue of *p*-bis(β -chloroethyl)aminobenzoic acid which did not react was filtered off and the filtrate acidified to pH 1. On cooling, crystals were slowly formed. The yield was 150 mg. (Table, Compound 7).

b) 560 mg of the chloride of *p*-bis(β -chloroethyl)aminobenzoic acid was dissolved in 5 ml of dry pyridine and then 300 mg of *l*-glutamic acid were added to the solution. The reaction mixture was kept gently boiling (bath temperature (130-135°) for four hours. In approximately two hours a heavy, oily precipitate came down which became solid on cooling.

M.P. 233-233.5° (from acetone). Yield 380 mg. Found %: N 10.02, 10.39; C 56.91, 56.63; H 5.18, 5.32; Cl 13.08, 13.20. $C_{26}H_{30}O_5N_4Cl_2$. Calculated %: N 10.20; C 56.83; H 5.46; Cl 12.93.

Condensation of the diethyl ester of *l*-glutamic acid and *p*-bis(β -chloroethyl)aminobenzoic acid in the presence of 1,3-dicyclohexylcarbodiimide. 2.4 g of the chloride of the diethyl ester of *l*-glutamic acid was dissolved in 10 ml of anhydrous alcohol and, after cooling with ice, 1.4 ml of triethylamine in 40 ml of absolute ether was added. The precipitate of triethylamine hydrochloride was filtered off and 2.6 g of *p*-bis(β -chloroethyl)aminobenzoic acid and a solution of 2.1 g of 1,3-dicyclohexylcarbodiimide in 10 ml of chloroform were added. The mixture was shaken and allowed to stand at room temperature overnight. The solvent was distilled off. The residue was a crystalline substance with a m.p. of 147-148°, weight 2 g; it was purified by chromatography: 500 mg of the compound was dissolved in 5 ml of benzene and the solution passed through a column containing Al_2O_3 (height of the layer 15 cm, diameter of the column 0.8 cm); development was done by means of benzene. 420 mg of compound (IV) with a m.p. of 152-153° was obtained.

Found %: C 61.49, 61.52; H 7.39, 7.56; N 9.01, 8.89; Cl 15.4, 14.98. $C_{24}H_{35}O_2N_3Cl_2$. Calculated %: C 61.54; H 7.47; N 8.97; Cl 15.2.

The diethyl ester of *p*-bis(β -chloroethyl)aminobenzoyl-*d,l*-glutamic acid. a) 1.6 g of the diethyl ester of *p*-aminobenzoyl-*d,l*-glutamic acid was dissolved in a mixture of 10 ml of glacial acetic acid and 5 ml of water. The solution was cooled to 0° and then 4 ml of ethylene oxide was added; the mixture was allowed to stand overnight at 20°. Then another 4 ml of ethylene oxide were added and the reaction mixture was kept for 24 hours at 20°. The solution was first neutralized to pH 5 by means of crystalline sodium carbonate and then to pH 7 by means of a saturated sodium carbonate solution. The oil that separated was extracted with chloroform, the chloroform extract was agitated with activated carbon, filtered and dried over calcined sodium sulfate. The chloroform was distilled in vacuo. The residue was an oil which was dried by means of an alcohol-benzene mixture (1 : 1). The oil was dissolved in 10 ml of anhydrous alcohol saturated with hydrogen chloride, mixed with activated carbon, filtered and poured into 100 ml of absolute ether. The hydrochloride which separated in the form of an oil was removed and dissolved in a mixture of dry benzene (10 ml) and dry chloroform (20 ml). 1.5 g of PCl_5 was added in portions, with cooling and stirring, to this solution, which was then boiled for 45 minutes until evolution of HCl ceased. The solvent and $POCl_3$ were distilled off in vacuo, and traces of $POCl_3$ were removed by blowing dry air through it. The residue was a resin-like mass which crystallized on prolonged standing in the refrigerator (Table, Compound 8).

b) 2.4 g of the hydrochloride of the diethyl ester of *l*-glutamic acid was dissolved in 5 ml of anhydrous alcohol and, after cooling with ice, 1.4 ml of triethylamine in 25 ml of absolute ether was added. The precipitate was filtered off and 2.25 g of the chloride of *p*-bis(β -chloroethyl)aminobenzoic acid and 1 ml of triethylamine were added.

The reaction mixture was boiled for 50 minutes, the precipitate which formed was filtered off and the solvent was distilled off in vacuo. The residue was an oil which crystallized on prolonged cooling.

SUMMARY

Five N-acyl derivatives of *l*-glutamic acid, not previously described in the literature, were synthesized.

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HYDROXY-DERIVATIVES OF γ -PYRONE

IV. THE PREPARATION OF ESTERS OF 5-HYDROXY- γ -PYRONE-2-CARBOXYLIC (COMENIC) ACID *

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The esters of acids of a number of derivatives of γ -pyrone were prepared in the majority of cases by the passage of hydrogen chloride into a mixture of the acid and the corresponding alcohol. The ethylester of comenic acid [3,4,7] was also prepared by this method. Its preparation by the decarboxylation of the diethyl ester of 3-hydroxy- γ -pyrone-2,6-dicarboxylic (meconic) acid is known [5,6]. Efforts to substitute sulfuric acid for hydrogen chloride were unsuccessful [4]. One of us found a method of preparing this ester in the presence of H_2SO_4 ; however, the reaction proceeds heterogeneously with the usual difficulties and gives a small yield.

One of us suggested [1] that it might be possible to esterify comenic acid under homogeneous conditions in solutions of sulfuric or orthophosphoric acid, with which it forms oxonium salts.

It should be noted that by means of physical-chemical methods of detection of oxonium compounds of comenic, meconic and chelidonic acids in aqueous solutions with boric acid, it was found [8] that they are formed only with the two latter acids, although not one of these oxonium compounds was actually separated. An effort by other authors [11] to prepare oxonium salts of chelidonic acid with mineral acids was also unsuccessful. The authors decided that the presence of carboxyl groups interferes with this.

An effort was made [9] to prepare the hydrochloride of comenic acid, but in vain; this was explained by the fact that comenic acid is insufficiently basic for this. Only the hydrochloride of 5-methoxy- γ -pyrone-2-carboxylic acid was obtained.

Despite this information in the literature, we found that comenic acid not only dissolves well in strong sulfuric acid and orthophosphoric acid, but also forms oxonium salts with them. Thus, when a saturated solution of comenic acid in sulfuric acid is kept in the refrigerator for 7-10 days, crystals are formed. We were able to separate this salt and the acid phosphate of comenic acid more simply and more rapidly by treatment with benzene.

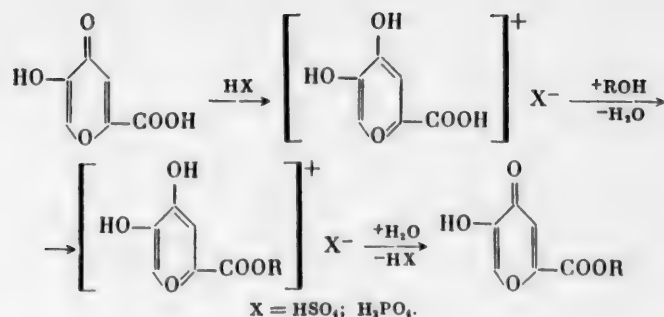
The acid sulfate and the acid phosphate of the ethyl ester of comenic acid were prepared by mixing solutions of the ethyl ester of comenic acid in benzene with the corresponding mineral acids in ether (the original reagents were taken in stoichiometric ratio with subsequent treatment with benzene).

The acid phosphate of comenic acid was separated from these salts with very great difficulty. It was very hygroscopic, as was also the acid phosphate of the ethyl ester of comenic acid. The neutral sulfate of the ethyl ester of comenic acid was the least hygroscopic. These oxonium compounds do not have characteristic melting points or decomposition temperatures.

Since the acid phosphate of comenic acid is the more stable on heating (it did not change color up to 210°), it is better to start from it in preparing the esters of comenic acid by prolonged heating, rather than from the sulfate of comenic acid. In some cases this salt is not satisfactory, for example in preparing the decyl ester. Moreover, on esterifying the phosphate of comenic acid, the reaction product is less tarry.

Preparation of the esters of comenic acid may be shown as follows:

*See previous communications [1,2].



In order to confirm this reaction mechanism we undertook some experiments in changing the order of mixing the reagents (the solution of the sulfate of comenic acid was added to the alcohol) in order to decompose the oxonium salt. It was evident that the reaction proceeded just the same as in the heterogeneous phase (Table 1, Exp. 1).

TABLE 1. Preparation of esters of comenic acid

No.	Temp.	Heating time (hr)	Alcohol concentration	Acid	Yield, %	Phase of the reaction mixture	No. of moles of alcohol	Note (alcohol)
1	110–115°	12.0	99.8	H ₂ SO ₄	55.0	Heterogeneous	10	Ethyl
2	100	2.5	Same	Same	68.0	Homogeneous	10	Same
3	100	3.0	Same	Same	70.0	Same	10	» »
4	100	2.5	95	H ₃ PO ₄	55.0	» »	10	» »
5	100	2.5	95	H ₂ SO ₄	60.0*	» »	6	» »
6	100	2.5	99.8	Same	55.0	» »	6	Isopropyl
7	100	2.5	99.5	Same	70.0	» »	10	Methyl
8	100	2.5	99.5	Same	35.0	» »	10	n-Propyl
9	100	2.5	99.8	Same	50.0	» »	10	n-Butyl
10	100	2.5	99.9	Same	40.0	» »	10	Isobutyl
11	100	2.5	99.9	Same	20.0	» »	6	n-Amyl
12	100	2.5	100	Same	20.0	» »	6	Isomyl
13	100	8.0	100	H ₃ PO ₄	20.0	» »	6	n-Decyl

* comenic acid.

From the data in the table it is evident that the esterification of comenic acid in the homogeneous phase proceeds more rapidly and with better yields. In the case of the esterification of comenic acid by azeotropic mixtures of ethyl and isopropyl alcohols it was shown that the corresponding esters are obtained in somewhat lower yields.

The esterification of oxonium salts of comenic acid proceeds smoothly and gives good yields both with primary and with secondary alcohols. We did not succeed in obtaining the corresponding ester with trimethylcarbinol. Apparently in this case the rule of N. A. Menshutkin on the esterification of esters holds true [10].

The acid phosphate of comenic acid also reacts easily with primary n-decyl alcohol to form the corresponding ester.

In all cases except one, comenic acid of the highest purity was used. In this case the yield of ester from technical comenic acid was lower, but not by much, if losses connected with its purification are taken into consideration.

EXPERIMENTAL

1. The acid sulfate of 5-hydroxy- γ -pyrone-2-carboxylic (comenic) acid 1.56 g of dry comenic acid was dissolved in 2 ml of H_2SO_4 (d 1.84) heated to 100° in a flask with a ground glass stopper; then 5 ml of benzene (b.p. $90-95^\circ$) was poured in and the flask placed in a refrigerator. The next day the viscous mass was stirred until a white precipitate formed and then it was cooled to -10° . After decanting the benzene it was washed three times with 5 ml of a mixture of ether and benzene (2 : 1). The precipitate was filtered off, washed with benzene and dried on a porous plate in a vacuum desiccator over P_2O_5 and paraffin. The yield was 2.2 g (90%). The decomposition temperature in a sealed capillary * was about 170° (with swelling and carbonization). The compound was hygroscopic, insoluble in benzene and alcohol and was decomposed by water into the original acid.

Found %: S 12.70 M 251. $\text{C}_6\text{H}_6\text{O}_9\text{S}$, Calculated %: S 12.60. M 254.

Colorless crystals that came down from the saturated solution of comenic acid in H_2SO_4 (d 1.84) after being kept in the refrigerator for ten days were separated, washed with benzene and dried as indicated above.

The decomposition temperature was the same.

2. The acid orthophosphate of comenic acid was prepared analogously from a solution of 1.56 g of comenic acid in 5.0 ml of H_3PO_4 (d 1.85, heated to 150°). The weight was approximately 2.0 g. The decomposition temperature was above 220° (with swelling and carbonization). The material was very hygroscopic.

0.1270 and 0.1220 g of the substance required 18.0 and 19.5 ml of 0.1 N NaOH (using bromthymol blue with phenolphthalein). A control titration required 20.0 ml of 0.1 N NaOH.

3. The acid sulfate of the ethyl ester of comenic acid. 0.28 ml of H_2SO_4 (d 1.84) diluted in 10 ml of anhydrous ether was poured into a hot solution of 0.92 g of the ethyl ester of comenic acid in 12 ml of dehydrated benzene in a flask with a ground stopper. After removing the solvent on an oil bath until the mass became viscous, it was treated with benzene which was decanted several times, and allowed to stand overnight in the refrigerator over benzene. The benzene was removed and some more of it was used for washing. The product was dried on a porous plate in a vacuum desiccator as mentioned above. The weight was about 1.2 g. The temperature was about 190° , with swelling. The material was hygroscopic M 287 (by titration); calc. 282.

4. The acid orthophosphate of the ethyl ester of comenic acid. This was obtained analogously to the acid sulfate from a solution of 0.55 g of the ethyl ester of comenic acid in 11 ml of benzene and 0.33 g of H_3PO_4 (d 1.85) in 5 ml of ether. The weight was about 0.7 g. The substance was hygroscopic.

0.1410 g of the substance required 15.4 ml of 0.1 N NaOH (using bromthymol blue with phenolphthalein); a control titration required 16.0 ml of 1.0 N NaOH.

5. The sulfate of the ethyl ester of comenic acid was prepared analogously to the acid sulfate from a solution of 1.84 g of ethyl ester in 25 ml of benzene and 0.28 ml of H_2SO_4 (d 1.84) in 10 ml of ether. The yield was 2.1 g (91.2%). The decomposition temperature was about 170° . The substance was hygroscopic M 461 (by titration); calculated, 466.

When the substance was decomposed with water, crystals with m.p. $126-127^\circ$ (from chloroform) were obtained which showed no depression of the melting point when mixed with a known sample of the ethyl ester of comenic acid. The previously reported m.p. 135° is incorrect [1,4].

6. The methyl ester of 5-hydroxy- γ -pyrone-2-carboxylic acid. 6.25 g of dry comenic acid and 9 ml of H_2SO_4 (d 1.84) were placed in a three-necked flask equipped with a reflux condenser, a dropping funnel and a mechanical stirrer **. After dissolving the acid at 100° , 12 ml of dehydrated methanol were added at 60° for 30 minutes and then heating was continued for 2.5 hours at 100° . The solution was poured over ice and the precipitate separated, washed with a minimum quantity of ice water and dried at 60° in vacuo. The precipitate was treated with 30 volumes of boiling CHCl_3 . The crystals that separated from the filtrate were washed with ice water. The yield was 4.9 g (70%).

* The decomposition temperature of other basic salts was also determined in a sealed capillary.

** All the esters described below were prepared in this equipment under the same conditions.

B.P. 185-186.5° (from CHCl_3). The crystals sublimed at 80°, dissolved easily in boiling water, alcohol and chloroform and with greater difficulty in cold water. A cherry-red color was formed with aqueous and alcohol solutions of FeCl_3 •

Found %: C 49.41; H 3.53. $\text{C}_7\text{H}_6\text{O}_5$, Calculated %: C 49.50; H 3.53.

The remaining esters (Table 2) were prepared in analogous fashion.

TABLE 2. The esters of comenic acid

Ester of comenic acid	M.p.	Empirical formula	Calc., %		Found, %		Note
			C	H	C	H	
Ethyl	126-127° from CHCl_3	$\text{C}_8\text{H}_8\text{O}_5$	52.10	4.35	52.29	4.50	From an azeotropic mixture (b.p. 87°)
n-Propyl	93-94° from water	$\text{C}_9\text{H}_{10}\text{O}_5$	54.61	5.55	54.66	5.28	
Isopropyl	154.5-156° from CHCl_3	$\text{C}_9\text{H}_{10}\text{O}_5$	54.61	5.55	54.16	4.94	From dehydrated alcohol (b.p. 81°)
n-Butyl	104-105° from CHCl_3	$\text{C}_{10}\text{H}_{12}\text{O}_5$	56.60	5.66	54.46	6.40	From primary alcohol
Isobutyl	95-96.5° from alcohol	$\text{C}_{10}\text{H}_{12}\text{O}_5$	56.60	5.66	56.40	6.20	from primary alcohol (b.p. 108°)
n-Amyl	97-98° from alcohol + CHCl_3	$\text{C}_{11}\text{H}_{14}\text{O}_5$	58.41	6.20	58.47	6.20	From primary alcohol (b.p. 138°)
Isoamyl	87-89° from CHCl_3	$\text{C}_{11}\text{H}_{14}\text{O}_5$	58.41	6.20	58.35	6.46	From primary alcohol (b.p. 132°)
n-Decyl	87-88° from CHCl_3	$\text{C}_{16}\text{H}_{24}\text{O}_5$	65.56	7.94	65.05	8.40	From primary alcohol

We express sincere thanks to A. S. Semenova and A. N. Larkina who did the microanalyses under the direction of A. D. Chinaeva.

SUMMARY

1. A method has been found which has not been described in the literature for esterifying 5-hydroxy- γ -pyrone-2-carboxylic acid (comenic), starting from its oxonium salts - the acid sulfate and the acid phosphate.

2. The oxonium salts of this acid, which have not been described in the literature, were separated: the acid sulfate and the acid orthophosphate, and also the acid sulfate, the acid phosphate and the sulfate of the ethyl ester of comenic acid.

3. The esters of comenic acid: methyl, n-propyl, isopropyl, (n-butyl)isobutyl, n-amyl, isoamyl and n-decyl, which have not been described in the literature, were prepared.

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ω -DIALKYLAMINOALKYL ESTERS OF 3,4,5-TRIMETHOXYBENZOIC ACID. II.

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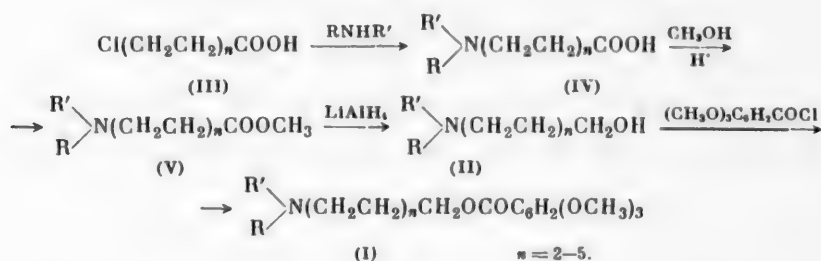
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In the preceding paper [1] we reported on the preparation of a series of ω -dialkylaminoalkyl esters of 3,4,5-trimethoxybenzoic acid (I) – compounds containing individual structural elements of reserpine. Some similar substances, according to the literature [2], have a tranquilizing action which is characteristic of this alkaloid. In view of the fact that neither we nor other authors [3] have yet been able to establish a connection between the intensity of the sedative activity of the esters (I) and the degree of their correspondence with the reserpine structure, we undertook the synthesis of esters (I) containing long alkyl chains and various basic substituents in the ω -position.

In order to prepare such esters it seemed desirable to find and make use of general methods of synthesis of α,ω -dialkylaminoalkanols (II) since the latter had previously been prepared by various methods depending on the length of the hydrocarbon chain: from ethylene oxide (for C_2) [4], from β -propiolactone [5, 6], from acrylonitrile [7, 8] or acrylic esters (for C_3) [8, 9], from tetrahydrofuran (for C_4) [10] or from tetrahydropyran (for C_5) [11]. For the preparation of longer chains the malonic synthesis [12] was used, or the conversion of α,ω -dibasic acids through α,ω -diols and α,ω -chloroalkanols to (II) [13, 14].

At the present time, thanks to the work of A. N. Nesmeyanov, R. Kh. Freidlina and their co-workers, the ω -chlorocarboxylic acids (III) are readily available, prepared by the telomerization of ethylene and carbon tetrachloride [15]. The availability of these compounds opens up new ways of synthesizing various types of α,ω -substituted aliphatic compounds, including α,ω -dialkylaminoalkanols (II). The esters of interest to us (I) were synthesized as follows.*



Many of the intermediate compounds (IV), (V) and (II) were prepared by us for the first time. The method is also suitable for the synthesis of the three carbon system (IV), (V) and (II) ($n=1$); however it is simpler to prepare the latter by other methods [5-9].

The substitution of the chlorine in ω -chlorocarboxylic acids (III) by the dialkylamino group was accomplished by heating one mole of the acid with three moles of dialkylamine at 95-100° in a closed vessel (in the case of piperidine a reflux condenser was used during heating). In the absence of water the reaction proceeds slowly, but when it is present 95% of the chlorine goes over into the ionic state within a few hours of heating the mixture on a boiling water bath. After distilling off the excess amine from the alkaline solution, acidifying and evaporation** the impure hydrochloride of ω -dialkylaminocarboxylic acid (IV) containing several percent of sodium chloride as an impurity

*This method permits the preparation of esters (I) containing aminoalkanol chains with an uneven number of carbon atoms.

**The chlorohydrate of ω -N-piperidyl enanthic acid may easily be separated from the reaction mixture by salting out.

TABLE 1. ω -Dialkylaminoacids

n	R	R'	method of preparation	Acid hydrochloride				Free		
				yield, %	M. p.	empirical formula	%Cl		monohy-	
							found	calc.	m. p.	empirical formula
1	CH ₃	CH ₃	A	65	187—189° [5]	C ₅ H ₁₁ O ₂ N · HCl	23.22	23.09	—	C ₅ H ₁₁ O ₂ N · H ₂ O
1	C ₂ H ₅	C ₂ H ₅	A	61	137—139 [5]	C ₇ H ₁₅ O ₂ N · HCl	19.47	19.52	—	C ₇ H ₁₅ O ₂ N · H ₂ O
1	—(CH ₂) ₅ —		B	78	212—214 [5]	C ₈ H ₁₅ O ₂ N · HCl	18.45	18.31	—	C ₈ H ₁₅ O ₂ N · H ₂ O
2	CH ₃	CH ₃	A	30	163—165 [17]	C ₇ H ₁₅ O ₂ N · HCl	19.76	19.52	84—85°	C ₇ H ₁₅ O ₂ N · H ₂ O
2	C ₂ H ₅	C ₂ H ₅	A	35	195—196.5 [17]	C ₉ H ₁₉ O ₂ N · HCl	16.90	16.91	63—64	C ₉ H ₁₉ O ₂ N · H ₂ O
2	—(CH ₂) ₅ —		A	40	203—204 [17]	C ₁₀ H ₁₉ O ₂ N · HCl	16.09	15.99	81—82	C ₁₀ H ₁₉ O ₂ N · H ₂ O
3	CH ₃	CH ₃	A	70	126—127	C ₉ H ₁₉ O ₂ N · HCl	17.20	16.91	83—85 **	C ₉ H ₁₉ O ₂ N · H ₂ O
3	C ₂ H ₅	C ₂ H ₅	A	71	98—99	C ₁₁ H ₂₃ O ₂ N · HCl	14.94	14.90	—	—
3	—(CH ₂) ₅ —		B	61	173—174	C ₁₂ H ₂₃ O ₂ N · HCl	14.08	14.26	70—71	C ₁₂ H ₂₃ O ₂ N · H ₂ O
4	CH ₃	CH ₃	B	86	137—138.5	C ₁₁ H ₂₃ O ₂ N · HCl	14.64	14.90	77—78	C ₁₁ H ₂₃ O ₂ N · H ₂ O
4	—(CH ₂) ₅ —		B	78	168—170	C ₁₄ H ₂₇ O ₂ N · HCl	12.99	12.77	53—55	C ₁₄ H ₂₇ O ₂ N · H ₂ O
5	CH ₃	CH ₃	B	70	136.5—138	C ₁₃ H ₂₇ O ₂ N · HCl	13.45	13.35	71—73	C ₁₃ H ₂₇ O ₂ N · H ₂ O

* Calculated on the impure hydrochloride of ω -dialkylaminoacid.

** Substance highly hygroscopic.

TABLE 2. Methyl Esters of ω -Dialkylaminocarboxylic Acids

n	R	R'	Base					
			yield, % ***	b. p. (press. in mm)	n_D^{20}	d_4^{20}	MR _D	
							found	calc.
2	CH ₃	CH ₃	70	80° (10) ****	1.4322	0.9212	44.86	44.62
2	C ₂ H ₅	C ₂ H ₅	95	75 (2)	1.4338	0.9095	53.61	53.87
2	—(CH ₂) ₅ —		96	100 (2.5)	1.4563	0.9592	56.51	56.27
3	CH ₃	CH ₃	72	88 (1.5)	1.4387	0.9179	53.57	53.87
3	C ₂ H ₅	C ₂ H ₅	73	90—91 (1)	1.4410	0.9041	62.94	63.23
3	—(CH ₂) ₅ —		50 *****	108 (1)	1.4611	0.9473	66.40	67.17
4	CH ₃	CH ₃	67	122—124 (3)	1.4372	0.8976	62.84	63.23
4	—(CH ₂) ₅ —		60	138—141 (2.5)	1.4652	0.9629	75.02	74.75
5	CH ₃	CH ₃	54	140—141.5 (3)	1.4415	0.8928	72.12	72.33
5	—(CH ₂) ₅ —		63	153 (1)	1.4638	0.9344	83.78	84.10

*** Calculated on the hydrochloride of ω -dialkylaminocarboxylic acid.

**** The literature shows b.p. 186—189° [18].

***** The crystalline hydrate has a m.p. of 63—65°.

***** Yield of the hydrochloride of the methyl ester of ω ,N-piperidylanthanic acid, calculated on the ω -chloroacid.

TABLE 1 (continued)



acid		anhydrous form							
drate		m.p.	empirical formula	% C		% H		% N	
found	calc.			found	calc.	found	calc.	found	calc.
—	—	—	C ₅ H ₁₁ O ₂ N	—	—	—	—	—	—
—	—	—	C ₇ H ₁₅ O ₂ N	—	—	—	—	—	—
—	—	—	C ₈ H ₁₅ O ₂ N	—	—	—	—	—	—
8.67	8.58	64—65°	C ₇ H ₁₅ O ₂ N	58.05	57.90	10.45	10.41	9.45	9.65
7.18	7.33	56—57	C ₉ H ₁₉ O ₂ N	62.46	62.38	11.09	11.05	8.10	8.09
7.07	6.89	69—71	C ₁₀ H ₁₉ O ₂ N	64.85	64.82	10.30	10.34	7.38	7.56
7.23	7.33	73—75 **	C ₉ H ₁₉ O ₂ N	—	—	—	—	8.20	8.09
—	—	Viscous mass	C ₁₁ H ₂₃ O ₂ N	65.35	65.67	11.41	11.44	7.30	6.96
6.00	6.06	51—52	C ₁₂ H ₂₃ O ₂ N	67.06	67.60	10.70	10.78	6.88	6.57
6.51	6.39	68—69	C ₁₁ H ₂₃ O ₂ N	—	—	—	—	7.16	6.96
5.60	5.40	47—48	C ₁₄ H ₂₇ O ₂ N	69.71	69.68	11.29	11.28	5.72	5.81
5.82	5.66	65—66	C ₁₃ H ₂₇ O ₂ N	68.09	68.08	11.65	11.87	5.96	6.11

TABLE 2 (continued)

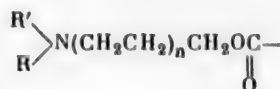


empirical formula	% N		Hydrochloride			Iodomethylate		
	found	calc.	m.p.	% Cl'		m.p.	% I'	
				found	calc.		found	calc.
C ₈ H ₁₇ O ₂ N	9.02	8.80	162—163°	17.95	18.11	131—132°	42.38	42.12
C ₁₀ H ₂₁ O ₂ N	7.60	7.47	60—61	16.08	15.92	90—91	38.80	38.54
C ₁₁ H ₂₁ O ₂ N	6.91	7.03	132—134	15.13	15.04	116—117	37.15	37.18
C ₁₀ H ₂₁ O ₂ N	7.27	7.47	86—87	15.94	15.92	102—103	38.77	38.54
C ₁₂ H ₂₅ O ₂ N	6.50	6.51	Viscous mass *****	14.55	14.34	Viscous mass	35.29	35.55
C ₁₃ H ₂₅ O ₂ N	6.49	6.17	120—121	13.45	13.42	72—73	34.71	34.41
C ₁₂ H ₂₅ O ₂ N	6.32	6.51	110—111	13.85	14.08	130—131	35.65	35.50
C ₁₅ H ₂₉ O ₂ N	5.67	5.49	120—121.5	12.03	12.14	69—70	32.10	31.94
C ₁₄ H ₂₉ O ₂ N	5.83	5.76	127—129	12.45	12.67	134—135	33.20	32.95
C ₁₇ H ₃₃ O ₂ N	5.00	4.94	131—132	10.98	11.09	92—93.5	29.95	29.83

TABLE 3. ω -Dialkylaminoalkanols

n	R	R'	Yield, % ***	b. p. (press. in mm)	m. p.	n_D^{20}	d_4^{20}	Base MR _b	
								found	calc.
2	CH ₃	CH ₃	85 *	113—114° (23)	—	1.4581	0.8943	40.15	39.99
2	C ₂ H ₅	C ₂ H ₅	78 **	116 (12)	—	1.4550	0.8828	48.99	49.23
2	—(CH ₂) ₅ —		81 ***	140 (13)	—	1.4821	0.9400	51.94	52.25
3	CH ₃	CH ₃	93	103 (2)	—	1.4492	0.8678	49.31	49.23
3	C ₂ H ₅	C ₂ H ₅	95 ****	107—108 (1)	—	1.4570	0.8810	57.93	58.48
3	—(CH ₂) ₅ —		96 *****	132—133 (2)	39—40°	—	—	—	—
4	CH ₃	CH ₃	97.5	103 (1.5)	—	1.4467	0.8574	58.33	58.48
4	—(CH ₂) ₅ —		86	—	50—51	—	—	—	—
5	CH ₃	CH ₃	71	—	29—30	—	—	—	—

TABLE 4. Dialkylaminoalkyl Esters of 3,4,5-Trimethoxybenzoic Acid



n	R	R'	Yield, % ***	b. p. (press. in mm)	m. p.	n_D^{20}	d_4^{20}	Base MR _b	
								found	calc.
2	CH ₃	CH ₃	62.5	183—185° (2)	—	1.5164	1.119	87.70	87.63
2	C ₂ H ₅	C ₂ H ₅	53	195—196 (1.5)	—	1.5117	1.098	96.52	96.86
2	—(CH ₂) ₅ —		62	199—201 (1)	—	1.5154	1.111	99.87	99.28
3	CH ₃	CH ₃	73	191—193 (1)	—	1.5110	1.092	96.87	96.86
3	C ₂ H ₅	C ₂ H ₅	67	224—226 (3)	—	1.5088	1.071	106.39	106.10
3	—(CH ₂) ₅ —		66	214—217 (2)	—	1.5183	1.098	108.60	108.52
4	CH ₃	CH ₃	74	205—207 (1)	29—30°	—	—	—	—
4	—(CH ₂) ₅ —		76	217—219 (1)	—	1.5104	1.075	117.80	117.75
5	CH ₃	CH ₃	58	—	33—34	—	—	—	—

* The literature [14] gives: b.p. 115–116° (25 mm); iodomethylate, m.p. 134°.

** The literature [12] gives: b.p. 131 (23–24 mm), n_D^{20} 1.4642, d_4^{20} 0.8842; hydrochloride m.p. 55–56°.

*** The literature [14] gives: b.p. 150–152 (22 mm); iodomethylate, m.p. 65–70°.

**** The literature [13] gives: b.p. 132° (9.5 mm), n_D^{20} 1.4561, d_4^{20} 0.8681.

***** The literature [19] gives: b.p. 144–147° (7 mm), n_D^{20} 1.4771, d_4^{20} 0.9253; hydrochloride m.p. 148–148.5°.

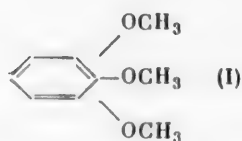
***** Substance highly hygroscopic.

TABLE 3 (continued)



empirical formula	% N		Hydrochloride			Iodomethylate		
			m. p.	% Cl'		m. p.	% I'	
	found	calc.		found	calc.		found	calc.
C ₇ H ₁₇ ON	10.80	10.68	92—94°	21.07	21.14	125.5—126.5°	46.74	46.44
C ₉ H ₂₁ ON	8.73	8.80	65—66	17.91	18.11	55—56	42.35	42.12
C ₁₀ H ₂₁ ON	7.88	8.18	148—149	17.15	17.07	71—72	40.89	40.52
C ₉ H ₂₁ ON	8.94	8.80	106—108	18.23	18.11	154.5—156	42.32	42.12
C ₁₁ H ₂₅ ON	7.71	7.48	75—76	15.94	15.86	Macno	38.71	38.53
C ₁₂ H ₂₅ ON	7.17	7.05	145—146	15.06	15.07	67—68	38.09	37.83
C ₁₁ H ₂₅ ON	7.51	7.48	120—121	16.06	15.86	156—158	38.75	38.53
C ₁₄ H ₂₉ ON	6.29	6.16	152.5—154	13.34	13.44	116—117.5	34.72	34.36
C ₁₃ H ₂₉ ON	6.57	6.50	139—141	14.03	14.08	167.5—169	35.43	35.50

TABLE 4 (continued)



empirical formula	% N		Hydrochloride			Iodomethylate		
			m. p.	% Cl'		m. p.	% I'	
	found	calc.		found	calc.		found	calc.
C ₁₇ H ₂₇ O ₅ N	4.45	4.32	101—102°	9.86	9.82	155—156°	27.19	27.20
C ₁₉ H ₃₁ O ₅ N	3.98	3.96	119—120	9.31	9.10	112—113.5	25.95	25.61
C ₂₀ H ₃₁ O ₅ N	3.86	3.83	151—152	8.96	8.82	137.5—138	25.30	25.01
C ₁₉ H ₃₁ O ₅ N	4.05	3.96	122—124	9.07	9.10	112—114	25.68	25.61
C ₂₁ H ₃₅ O ₅ N	3.64	3.67	93—94	8.51	8.48	96—97	24.35	24.24
C ₂₂ H ₃₅ O ₅ N	3.60	3.56	110—111	8.38	8.25	123—125	24.30	23.69
C ₂₁ H ₃₅ O ₅ N	3.74	3.67	107—108.5	8.38	8.48	106—107	24.01	24.24
C ₂₄ H ₃₉ O ₅ N	3.29	3.32	*	—	—	115—116	22.58	22.52
C ₂₃ H ₃₉ O ₅ N	3.64	3.42	104—106	7.98	7.95	69—70	22.82	23.00

was obtained. This substance was used for the subsequent syntheses without further purification. Analytically pure samples of the hydrochlorides were prepared by recrystallizing them from the free acids (IV); separation of the latter from the impure hydrochloride is most easily achieved by the use of the ion-exchange resin KU-1 [16]. It should be noted that ω -dialkyldiaminocarboxylic acids (IV) crystallize from solutions containing water in the form of monohydrates which have higher melting points than the anhydrous acids; in a number of cases the drying process goes through a liquid eutectic mixture at room temperature. Conversion of acid (IV) into the methyl ester (V) was accomplished by the usual methods in the presence of sulfuric acid or hydrogen chloride. In some cases, for example for (IV), $n=2$, $R=R'=(CH_2)_6$, even heating a methanol solution of the hydrochloride (IV) to boiling led to the formation of the hydrochloride of the ester (V). Reduction of the esters (V) by means of lithium aluminum hydride gives ω -dialkylaminoalcohols (II) in high yields (80-90%). The esters (I) were obtained by the reaction of the chloride of 3,4,5-trimethoxybenzoic acid with 630 moles of dialkylaminoalkanol in benzene solution.

Compounds (I), (II) and (V) were characterized as the hydrochlorides and iodomethylates; information on these substances is shown in Tables 1-4*. Typical experimental conditions are given under EXPERIMENTAL. Results on the pharmacological study of the esters (I) will be reported on separately.

EXPERIMENTAL

I. Preparation of ω -dialkylaminocarboxylic acids (see Table 1)

a) Preparation of hydrochlorides. A mixture of 1 g mole of ω -chlorocarboxylic acid, 3 g moles of dialkylamine and 250 ml of water were heated in a closed vessel for six hours at 95-100°. The reaction mixture was made alkaline with a solution of caustic soda and the dialkylamine steam distilled. The material remaining in the flask was acidified until it showed an acid reaction to Congo; then it was heated with carbon, filtered, and the water distilled off under the vacuum of a water pump at a temperature not above 50° (method A). The remainder was treated with methanol, the sodium chloride was filtered off, the filtrate evaporated in vacuo and the yield of the hydrochloride of ω -dialkylaminocarboxylic acid determined by the percent of ionic chlorine in the material remaining. In order to obtain analytically pure samples of the hydrochlorides, the precipitate was treated with acetone, methanol or mixtures of them. In some cases (method B), immediately after distilling off two thirds of the water and cooling, crystallization of the hydrochloride of ω -dialkylaminocarboxylic acid began, which was filtered off and purified by the solvents mentioned above.

b) Preparation of free ω -dialkylaminocarboxylic acids. A solution of 5 g of impure hydrochloride of ω -dialkylaminocarboxylic acid in 100 ml of water was passed through a column 20 mm in diameter containing 50 g of the air-dry ion-exchange resin KU-1; the contents of the column were washed with water until it no longer showed a test for the chlorine ion, and then with a 5% solution of ammonia (the volume of wash solution bore a 100 : 1 ratio to the weight of hydrochloride). The wash solution was treated with carbon and evaporated to dryness in vacuo. The yields of the ω -dialkylaminocarboxylic acids amounted to about 90%. For analysis the substance was recrystallized from aqueous acetone and dried in the air without heating, thus forming monohydrates. Dehydrated aminoacids were prepared by drying the monohydrates in vacuo over sulfuric acid.

II. Preparation of the methyl esters of ω -dialkylaminocarboxylic acids (see Table 2)

The methyl ester of ω -dimethylaminovalerianic acid. 50 ml of concentrated H_2SO_4 was added to a solution of 54.5 g of impure chlorohydrate of ω -dimethylaminovalerianic acid in 300 ml of methanol; the mixture was heated at the boiling point under a reflux condenser for six hours, and then the methanol was distilled off in vacuo. To this material, after cooling, were added 100 ml of water and a solution of caustic soda until phenolphthalein showed an alkaline reaction; the solution was extracted with ether and the material remaining after distilling off the ether was distilled in vacuo. 41.8 g of the methyl ester of ω -dimethylaminocarboxylic acid was obtained (Table 2, $n=2$, $R=R'=CH_3$).

The hydrochloride. An ether solution of hydrogen chloride was added to 1 g of the base in 20 ml of ether until it showed an acid reaction to Congo. The precipitate formed was washed with acetone and recrystallized from acetone.

Iodomethylate. 3 ml of methyl iodide was added to a solution of 1 g of the base in 10 ml of acetone; the precipitate of iodomethylate was washed with acetone and recrystallized from acetone.

*In all tables the column showing the analytical results gives the average value of two determinations.

The methyl ester of ω -dimethylaminopelargonic acid. A solution of 20 g of impure chlorohydrate of ω -dimethylaminopelargonic acid in 150 ml of methanol was saturated with hydrogen chloride in the cold. After standing overnight the methanol was distilled from the reaction mixture in vacuo, the residue dissolved in water, made alkaline with a solution of caustic soda and extracted with ether. After removing the ether the remaining material was distilled in vacuo. (Table 2, $n=4$, $R=R'=\text{CH}_3$)

The hydrochloride of the methyl ester of ω , N-piperidylanthanic acid. The reaction product of 48 g of ω -chloroanthanic acid and 76 g of piperidine, after removal of the piperidine and acidification (method A) was saturated with sodium chloride. The mixture of the hydrochloride of ω , N-piperidylanthanic acid and sodium chloride that precipitated was filtered off and dried (weight 120 g); 250 ml of methanol was added and the mixture was heated to boiling for two hours. The sodium chloride was filtered off and washed with methanol. The crystalline precipitate of the methyl ester of ω , N-piperidylanthanic acid which was obtained after removing the methanol from the combined filtrates was recrystallized from 250 ml of acetone. 37.8 g (50% calculated on the ω -chloroacid) of the hydrochloride of the ester were obtained [Table 2, $n=3$, $R=R'=(\text{CH}_2)_5$].

III. Preparation of ω -dialkylaminoalkanols (see Table 3)

ω -N-(Piperidyl)-nonanol. A solution of 7.7 g of the methyl ester of ω , N-piperidylpelargonic acid in 50 ml of ether was added drop by drop at 10-15° to 30 ml of a 0.5 N ether solution of lithium aluminum hydride. After stirring the reaction mixture for two hours at room temperature and cooling, 1.5 ml of water was added. The precipitate consisting of the hydroxides of aluminum and lithium was filtered off, the ether solution dried, the ether removed and the remaining crystalline material recrystallized from petroleum ether. The yield was 5.7 g [Table 3, $n=4$, $R=R'=(\text{CH}_2)_5$].

IV. Preparation of ω -dialkylaminoalkyl esters of 3,4,5-trimethoxybenzoic acid (see Table 4)

ω -Dimethylaminononyl ester of 3,4,5-trimethoxybenzoic acid. 3.41 g of the chloride of 3,4,5-trimethoxybenzoic acid in 40 ml of benzene was added drop by drop during the course of an hour to a boiling solution of 5.62 g of ω -dimethylaminononanol in 30 ml of benzene. The boiling mixture was stirred for three hours; after cooling, the hydrochloride of ω -dimethylaminononanol was filtered off and the remaining material distilled in vacuo (Table 4, $n=4$, $R=R'=\text{CH}_3$).

SUMMARY

A number of ω -dialkylaminoalkyl esters of 3,4,4-trimethoxybenzoic acid were prepared. A general method for synthesizing ω -dialkylaminoalkanols with an uneven number of carbon atoms from the corresponding ω -chlorocarboxylic acids was worked out.

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CHEMISTRY OF FLUORENE

1. NEW 2,3,7-DERIVATIVES OF FLUORENE

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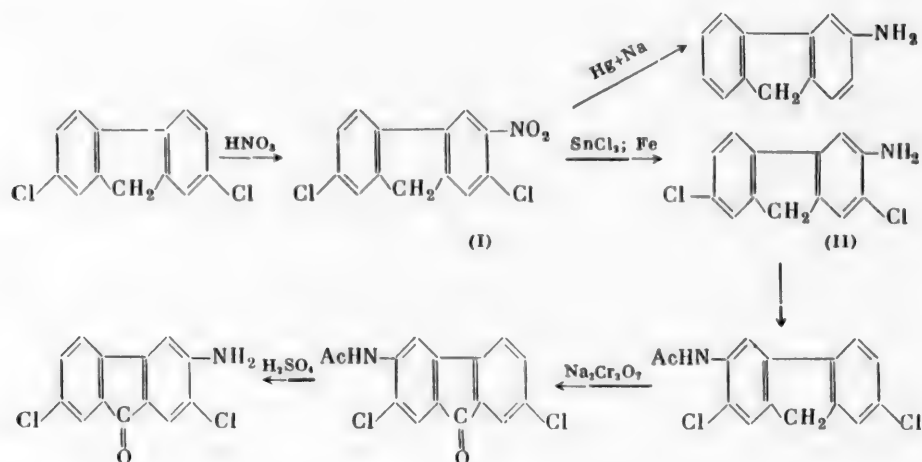
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In the literature there are reports on the nitration of 2-halogenofluorenes with the formation of 2-halogeno-7-nitro derivatives [1] and there are absolutely no data on the nitration of 2,7-dihalogeno derivatives of fluorene. When substituents are introduced into 2,7-substituted fluorenes in the overwhelming majority of cases 2,3,7-trisubstituted fluorenes are formed, but sometimes a small amount of 1,2,7-derivative is isolated [2,3].

Taking into consideration that it is possible to prepare various compounds from the nitro derivatives through the amines, we investigated the nitration of 2,7-dichlorofluorene to 2,7-dichloro-3-nitrofluorene (I) so that after converting it to the amine we could synthesize a number of derivatives. By the reduction of (I) with sodium amalgam to 3-aminofluorene with simultaneous elimination of chlorine we determined the position of the nitro group. Reduction of (I) with stannous chloride or iron powder leads to the formation of 2,7-dichloro-3-aminofluorene (II), for which a number of derivatives substituted on the nitrogen have been prepared. By oxidation with sodium dichromate of the fluorene derivatives that had been prepared, the corresponding fluorenones were synthesized. The reactions that we studied can be represented by the following scheme:



EXPERIMENTAL

Preparation of 2,7-dichloro-3-nitrofluorene (I). In a three-necked flask fitted with a dropping funnel, mechanical stirrer, and thermometer and set in a water bath were placed 15 g of 2,7-dichlorofluorene and 270 ml of glacial acetic acid. Over the course of 20 minutes a nitrating mixture consisting of 15 ml of nitric acid (d 1.43) and 15 ml of sulfuric acid (d 1.83) was added at 35° , then in 25 minutes the temperature was raised to 70° , and the reaction mixture was kept at this temperature for 15 minutes, after which it was cooled. The precipitate that had separated out was filtered off and washed on the filter with a 2% solution of sodium acetate in glacial acetic acid, then with water. The weight of the crude product was 16 g M.p. $179-180^\circ$ (from glacial acetic acid). After recrystallization 13.7 g of 2,7-dichloro-3-nitrofluorene was obtained.

Found %: N 4.85, 4.91; Cl 25.66, 25.79, $C_{13}H_7O_2NCl_2$. Calculated %: N 4.99; Cl 25.34.

Reduction of 2,7-dichloro-3-nitrofluorene. a) With sodium amalgam. To 2 g of 2,7-dichloro-3-nitrofluorene in 250 ml of alcohol was gradually added 140 g of 4% sodium amalgam and the mixture was heated at 65° for 45 minutes. The hot solution was separated from the mercury and precipitated with water. The precipitate was filtered off, dried, and crystallized from benzene. The precipitate that separated out was filtered off, dissolved in xylene, and purified by chromatographing on alumina.

Fifteen grams of 3-aminofluorene was obtained with m.p. 148.5-150° (according to the data in [4] 149-150°).

Found %: N 7.55, 7.67. $C_{13}H_{11}N$. Calculated %: N 7.72.

b) With iron powder. In a three-necked flask fitted with a mechanical stirrer and reflux condenser and placed in a water bath, 12.7 g of 2,7-dichloro-3-nitrofluorene was dissolved in 210 ml of alcohol, 15 g of chemically pure iron powder reduced with hydrogen was introduced, and over a period of 2 hours 300 ml of concentrated hydrochloric acid was added dropwise with vigorous boiling of the reaction mixture. The flask was heated on the water bath for another 3 hours, then cooled, the precipitate that had separated out was filtered off, washed with hydrochloric acid, with water, then with 2% sodium hydroxide solution, and again with water, and 11.5 g of material was obtained. After recrystallization the m.p. was 151-152° (from aqueous alcohol, decomp.). The weight of pure 2,7-dichloro-3-aminofluorene (II) was 9.2 g.

Found %: N 5.80, 5.71; Cl 29.28, 28.31. $C_{13}H_9NCl_2$. Calculated %: N 5.59; Cl 28.35.

c) With stannous chloride. A mixture of 1.5 g of 2,7-dichloro-3-nitrofluorene, 30 ml of alcohol, 4.5 g of stannous chloride, and 5 ml of concentrated hydrochloric acid was boiled for 30 minutes, 20 ml of 25% sulfuric acid was added, the precipitate that separated out was filtered off and boiled with 5% sulfuric acid, then the amine was separated in 70% yield by the addition of ammonia.

Acetylation of 2,7-dichloro-3-aminofluorene. A mixture of 2.2 g of 2,7-dichloro-3-aminofluorene, 4 ml of acetic anhydride, and 50 ml of glacial acetic acid was heated on a glycerol bath at 110-115° for 1 hour, then the reaction mixture was poured into water, and the precipitate was filtered off. M.p. 256-257° (from glacial acetic acid, decomp.). Yield of 2,7-dichloro-3-acetamidofluorene 1.8 g.

Found %: N 4.69, 4.78; Cl 23.98, 24.12 $C_{15}H_{11}ONCl_2$. Calculated %: N 4.71; Cl 24.22.

Benzoylation of 2,7-dichloro-3-aminofluorene. One gram of 2,7-dichloro-3-aminofluorene was dissolved in a mixture of 10 ml of pyridine and 20 ml of benzene and 1 ml of benzoyl chloride was added drop by drop. The reaction mixture was heated for 45 minutes on a water bath at 60-70°, then poured into water, the precipitate that had separated was filtered off, the benzene layer of the filtrate was separated, the benzene was distilled off and the residue was combined with the previously filtered precipitate. M.p. 270-271° (from glacial acetic acid, decomp.). Weight of 2,7-dichloro-3-benzamidofluorene 1.1 g.

Found %: N 3.87, 3.92; Cl 19.72, 19.82. $C_{20}H_{13}ONCl_2$. Calculated %: N 3.94; Cl 19.98.

Preparation of 2,7-dichloro-3-(p-toluenesulfonamido) fluorene. One gram of 2,7-dichloro-3-aminofluorene and 1.1 g of p-toluenesulfonyl chloride were dissolved in 50 ml of glacial acetic acid and over the course of 5 minutes 1.5 g of fused sodium acetate was added. The reaction mixture was heated for 2 hours on a glycerol bath at 110° and left overnight, then poured into water and the precipitate was filtered off. M.p. 259-260° (from glacial acetic acid, decomp.). Yield 0.7 g of 2,7-dichloro-3-(p-toluenesulfonamido) fluorene.

Found %: N 3.42, 3.46; Cl 17.56, 17.60. $C_{20}H_{15}O_2NSCl_2$. Calculated %: N 3.48; Cl 17.69.

2,7-Dichloro-3-(p-nitrobenzamido)fluorene was prepared by a similar method in 75% yield. M.p. 298-299° (decomp.).

Found %: N 6.86, 6.94; Cl 17.63, 17.71. $C_{20}H_{12}O_3N_2Cl_2$. Calculated %: N 6.99; Cl 17.74.

Oxidation of 2,7-dichloro-3-nitrofluorene to 2,7-dichloro-3-nitro-fluorenone. In a three-necked flask fitted with a mechanical stirrer and reflux condenser 2.8 g of 2,7-dichloro-3-nitrofluorene was dissolved in 115 ml of glacial acetic acid and over the course of 20 minutes 12 g of sodium dichromate was added. The reaction mixture was heated on a water bath for 2 hours, cooled, and poured into water. The precipitate that separated out was filtered off and heated with 200 ml of 5% sulfuric acid. M.p. 184-185° (from glacial acetic acid). Yield of 2,7-dichloro-3-nitro-fluorenone 2.3 g.

Found %: N 4.69, 4.72; Cl 24.10, 24.08. $C_{13}H_5O_3NCl_2$. Calculated %: N 4.75; Cl 24.14.

By a similar method 2,7-dichloro-3-acetamidofluorenone was obtained with m.p. 306-307° (decomp.). Yield 85%.

Found %: N 4.49, 4.52; Cl 23.92, 23.00. $C_{15}H_9O_2NCl_2$. Calculated %: N 4.55; Cl 23.11.

2,7-Dichloro-3-benzamidofluorenone was similarly prepared with m. p. 285-286° (decomp.). Yield 87%.

Found %: N 3.59, 3.70; Cl 18.98, 19.11. $C_{20}H_{11}O_2NCl_2$. Calculated %: N 3.79; Cl 19.22.

2,7-Dichloro-3-(p-toluenesulfamido)fluorenone was similarly prepared with m.p. 309-310° (decomp.). Yield 78%.

Found %: N 3.29, 3.32; Cl 16.95, 16.90. $C_{20}H_{13}O_3NSCl_2$. Calculated %: N 3.36; Cl 17.07.

2,7-Dichloro-3-(p-nitrobenzamido)fluorenone was similarly prepared with m.p. 310-311° (decomp.). Yield 88%.

Found %: N 6.54, 6.41; Cl 17.02, 17.10. $C_{20}H_{10}O_4N_2Cl_2$. Calculated %: N 6.51; Cl 17.13.

Preparation of 2,7-dichloro-3-aminofluorenone. To 1.5 g of 2,7-dichloro-3-acetamidofluorenone were added 70 ml of concentrated sulfuric acid and 5 ml of water, the flask was heated for 4 hours at 80-85°, then its contents were poured into water, the precipitate that separated out was filtered off, washed with water, with 2% sodium hydroxide solution, and again with water. M. p. 208-209° (from aqueous alcohol, decomp.). Yield of 2,7-dichloro-3-aminofluorenone 1.2 g.

Found %: N 5.24, 5.29; Cl 26.70, 26.72 $C_{13}H_7ONCl_2$. Calculated %: N 5.28; Cl 26.79.

SUMMARY

1. Methods have been developed for the preparation of 2,7-dichloro-3-nitro- and 2,7-dichloro-3-aminofluorene and also for the corresponding fluorenones.
2. The position of the nitro group in 2,7-dichloro-3-nitrofluorene was demonstrated.
3. Twelve derivatives of fluorene which had not been described in the literature were synthesized.

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ISOMERISM OF N-ARYLMALEIMIDES

A. E. Kretov, N. E. Kyl'chitskaya, and A. F. Mal'nev

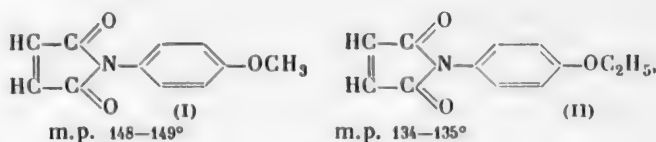
Dnepropetrovskii Chemico-Technological Institute

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 8,

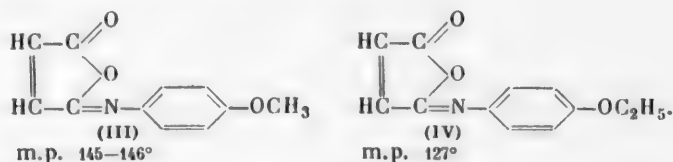
pp. 2588-2594, August 1961

Original article submitted July 22, 1960

The hypothesis of the possibility of isomerism of the N-arylmaleimides was first expressed by Piutti [1]. He synthesized derivatives of N-p-methoxy- and N-p-ethoxyphenylmaleamido acids in two forms. He ascribed to the colored form the symmetrical structures (I, II).

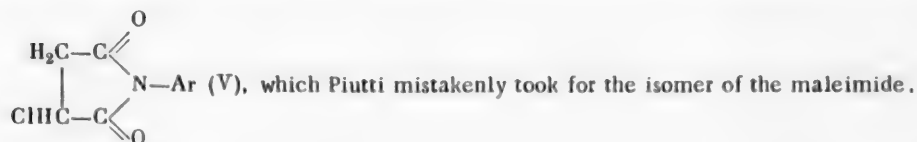


and to the colorless form the unsymmetrical structures (III, IV).



The colored compound of symmetrical structure was synthesized by Piutti by the dehydration of the corresponding N-arylmaleamido acid with phosphorus pentoxide. The colorless compound with the hypothetical unsymmetrical structure was prepared by him by dehydration of the same acid with acetyl chloride.

William and Roderick [2] repeated Piutti's work and showed that the colored form corresponded to the maleimide of symmetrical structure, while the colorless form was not the N-arylmaleimide, but α -chloro-N-arylsuccinimide (V),



α -Chloro-N-p-methoxyphenylsuccinimide and α -chloro-N-p-ethoxyphenylsuccinimide, synthesized by the addition of hydrogen chloride to the corresponding N-arylmaleimides [3], turned out, as we proved, to be identical with the compounds obtained by the reaction of the N-arylmaleamido acids with acetyl chloride.

Consequently the isomaleimides were not obtained by the methods of Piutti, Hoogewerff, and von Dorp [4].

The possibility of the existence of the isomaleimides was confirmed by the synthesis of N-(4-hydroxy-1-naphthyl) isomaleimide from the corresponding maleamido acid in the presence of trifluoroacetic anhydride [5]. We should mention the existence of isomerism in the structurally similar derivatives of phthalimide and isophthalimide [6].

In the present work the isomerism of the N-arylmaleimides has been demonstrated. We have found the reaction conditions for the dehydration of some N-arylmaleamido acids and have prepared compounds with the same molecular weight and composition, which differ in color, crystalline form, and melting point.

TABLE 1. Maleimides

Compound	Empirical formula	Reaction temperature*	Yield (in %)	Melting point	M		% N	
					found	calc.	found	calc.
N-p-Methoxyphenylmaleimide	C ₁₁ H ₉ O ₃ N	90—95°	80	148—149°[1, 2, 7]	206	203	6.82	6.89
N-p-Ethoxyphenylmaleimide	C ₁₂ H ₁₁ O ₃ N	95—100	79	134—135[1, 7]	219	217	6.5	6.45
N-4-Chloro-2-methylphenylmaleimide	C ₁₁ H ₈ O ₂ NCl	75—80	82	68[3]	219	221.5	6.29	6.32
N-5-Chloro-2-methoxyphenylmaleimide	C ₁₁ H ₈ O ₃ NCl	95—100	83	147—148 Yellow crystals	234.9	237.6	5.92	5.89
N-5-Nitro-2-methoxyphenylmaleimide	C ₁₁ H ₈ O ₅ N ₂	95—100	82	146—147 Colorless needle-shaped crystals	252	248	11.1	11.28

*Reaction time 20-30 min.

TABLE 2. Isomaleamides

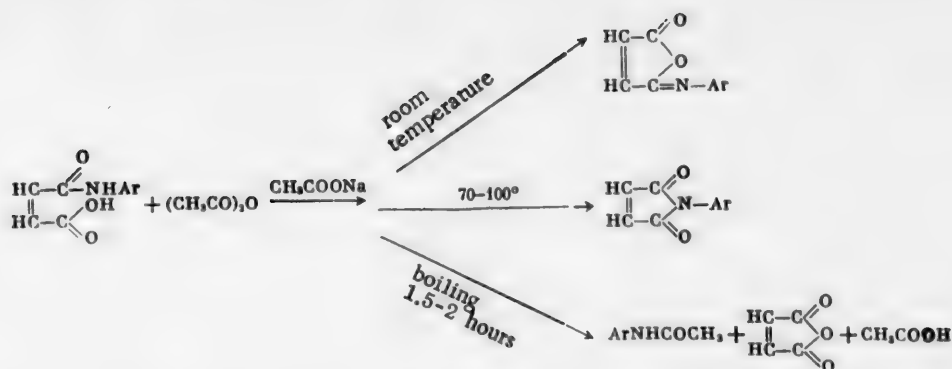
Compound	Empirical formula	Reaction conditions		Yield (in %)	Melting point	M		% N	
		temp.	time (in min)			found	calc.	found	calc.
N-p-Methoxyphenylisomaleimide	C ₁₁ H ₉ O ₃ N	73—76°	1—2	90	68.5—69°	196.9	203	7.1	6.89
N-p-Ethoxyphenylisomaleimide	C ₁₂ H ₁₁ O ₃ N	83—85	2—3	87	74—75	211	217	6.5	6.45
N-4-Chloro-2-methylphenylisomaleimide	C ₁₁ H ₈ O ₂ NCl	48—50	2—3	89	39—40	218.5	221.5	6.4	6.32
N-5-Chloro-2-methoxyphenylisomaleimide	C ₁₁ H ₈ O ₃ NCl	55—58	1—2	92	115—116	233	237.6	5.83	5.89

In the present work the isomerism of the N-arylmaleimides has been demonstrated. We have found the reaction conditions for the dehydration of some N-arylmaleamido acids and have prepared compounds with the same molecular weight and composition, which differ in color, crystalline form, and melting point.

The data on the synthesis of the symmetrical maleimides are given in Table 1 and those for the unsymmetrical compounds in Table 2.

The products of hydrolysis of the N-arylmaleimides and the N-arylismaleimides in both cases were the corresponding N-arylmaleamido acids, which was established by a mixed [melting point] test.

The direction of reaction of the N-arylmaleamido acids with acetic anhydride and the formation of the isomeric N-arylmaleimides can be represented in the general form by the following diagram.



Upon heating to 100° in acetic anhydride solution the isomaleimides go over to the symmetrical maleimides.

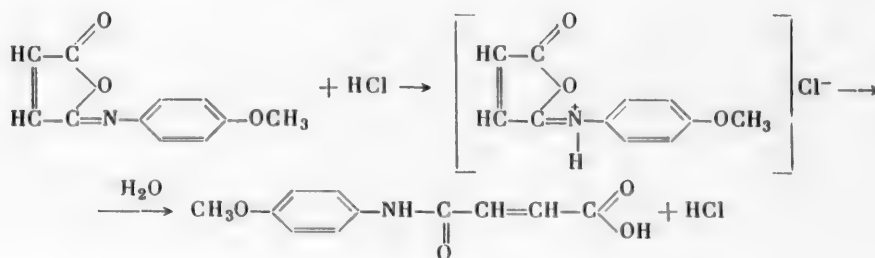
We were not able, however, to obtain isomaleimides from all of the N-arylmaleamido acids that were investigated. From such acids as N-phenylmaleamido, N-p-, -m-, and -o-nitrophenylmaleamido and N-5-nitro-2-methoxyphenylmaleamido acids we did not succeed in isolating the unsymmetrical forms of the imides.

The maleimides and isomaleimides differ with respect to both their physical and their chemical properties.

The reaction of the isomers with hydrogen chloride is very curious. When a symmetrical N-arylmaleimide reacts with hydrogen chloride, the already known reaction [3] forming the α-chloro-N-arylsuccinimide (V) takes place.

The reaction of an unsymmetrical N-arylmaleimide with hydrogen chloride leads to the formation of another, easily hydrolyzed, colored product, which differs from the corresponding α-chloro-N-arylsuccinimide in its melting point.

The products of the reaction of the isomaleimides with hydrogen chloride are very easily hydrolyzed with the formation of the corresponding N-arylmaleamido acids, while the compounds (V) are not hydrolyzed under ordinary conditions. Apparently the isomaleimides, which have basic properties, form salts with hydrogen chloride which are easily hydrolyzed to the N-arylmaleamido acids.



When hydrogen chloride is passed through an acetic acid solution of an N-arylmaleimide for several hours and the mixture is allowed to stand overnight, the hydrochloride is completely converted to the α-chloro-N-arylsuccinimide (V).

For additional identification of the compounds obtained we investigated the infrared absorption spectra of the two isomeric forms of N-p-methoxy- and N-p-ethoxyphenylmaleimides. *

The spectrum of the symmetrical N-p-sthoxyphenylmaleimide (Fig. 2). The spectra of the unsymmetrical N-p-methoxy-unsymmetrical N-p-methoys- and N-p-ethoxy-phenylmaleimides also were similar to one another (Figs. 3, 4).

*The spectra were determined in the Institute of Physics of the Academy of Sciences of the Ukrainian SSR with a VIKS-3 vacuum infrared spectrometer (NaCl prism). The samples for the determinations were prepared in the form of suspensions in vaseline oil, and the thickness of the absorbing layer was 50-60μ.

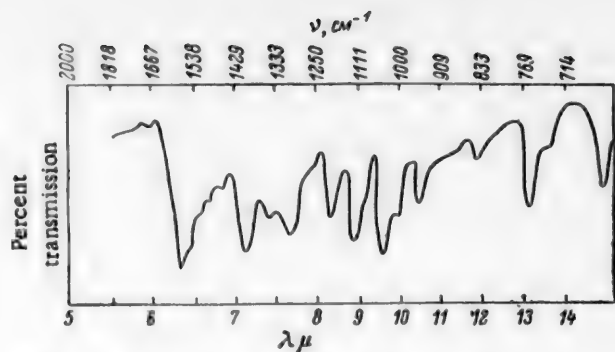


Fig. 1. IR spectrum of N-p-methoxyphenylmaleimide

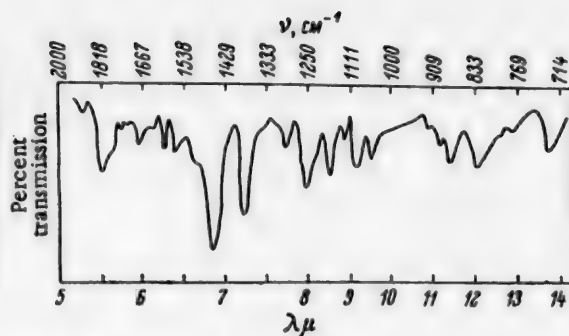


Fig. 2. IR spectrum of N-p-ethoxyphenylmaleimide

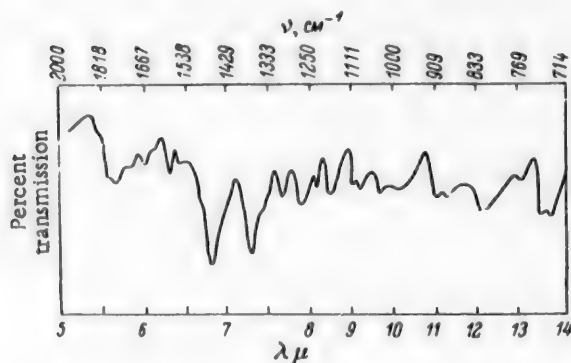


Fig. 3. IR spectrum of N-p-methoxyphenylisomaleimide

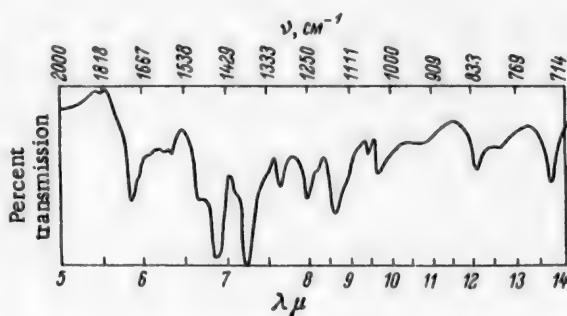


Fig. 4. IR spectrum of N-p-ethoxyphenylisomaleimide

The most interesting region is $1800\text{--}1550\text{ cm}^{-1}$, in which the absorption bands due to the valence vibrations of the >C=O , >C=N- , >C=C< groups are located [8].

In the case of the symmetrical N-p-methoxy- and N-p-ethoxyphenylmaleimides an intense band is observed in the region of 1715 cm^{-1} with a shoulder at 1684 cm^{-1} , which corresponds to the vibration of the >C=O group in the symmetrical five-membered ring of (I) and (II) [8,9], and there also are weaker bands in the region $1670\text{--}1540\text{ cm}^{-1}$.

For the unsymmetrical compounds, the absence of the intense band at 1715 cm^{-1} is characteristic, and the absorption maximum is shifted to the shorter wave portion of the spectrum, to 1800 cm^{-1} .

Study of the valence vibrations of the >C=N group was difficult, since they appear in the same region of the spectrum as the vibrations of >C=O , but the general aspect of the absorption spectrum in the region $1830\text{--}1650\text{ cm}^{-1}$ may be characteristic of symmetrical and unsymmetrical samples.

For the unsymmetrical samples bands appear clearly in the region $1600\text{--}1540\text{ cm}^{-1}$ and new bands are observed at $910\text{--}840\text{ cm}^{-1}$ which are due to the skeletal vibrations of the molecule.

EXPERIMENTAL

N-5-Chloro-2-methoxyphenylmaleamido and N-5-nitro-2-methoxyphenylmaleamido acids were prepared from the corresponding amines and maleic anhydride by a previously described method [10]. N-5-Chloro-2-methoxyphenylmaleamido acid was a yellow crystalline material with m.p. $167\text{--}168^\circ$.

Found M 256.4. $\text{C}_{11}\text{H}_{10}\text{O}_4\text{NCl}$. Calculated M 255.5.

N-5-Nitro-2-methoxyphenylmaleamido acid was a colorless crystalline material with m.p. 178-179°.

Found M 266.8. $C_{11}H_{10}O_6N_2$. Calculated M 266.2

The symmetrical N-arylmaleimides were prepared from the corresponding N-arylmaleamido acids and acetic anhydride in the presence of sodium acetate by a method developed by us [3] (Table 1).

The unsymmetrical N-arylmaleimides (N-arylisomaleimides) were synthesized from the N-arylmaleamido acids and acetic anhydride in the presence of sodium acetate under mild conditions, at room temperature or with careful heating.

To 0.05 mole of N-p-methoxyphenylmaleamido acid were added 0.05 mole of sodium acetate and 0.5 mole of acetic anhydride. The reaction mixture in the form of a suspension was left to stand at room temperature for 30 hours until a homogeneous solution formed, which was poured into ice water and neutralized with sodium bicarbonate. After careful washing, the product was dried. Yield of crude product 84%. By recrystallization from acetone and water the pure compound was obtained in the form of yellow needles, readily soluble in acetone, benzene, alcohol, carbon tetrachloride, and ether.

N-p-Ethoxyphenylisomaleimide was prepared in a similar manner in the form of light yellow prisms.

Other N-arylisomaleimides were prepared by careful heating of the corresponding N-arylmaleamido acids with 4 times the molar quantity of acetic anhydride in the presence of sodium acetate. The reaction mixture was heated to a definite temperature and held at this temperature for 2-3 minutes (Table 2).

Hydrolysis of two isomeric forms of the imides. One-tenth mole of N-4-chloro-2-methylphenylmaleimide and the same amount of the corresponding isomaleimide were heated in the same manner with 25 ml of 1 N NaOH for 15 minutes. The solutions were cooled, precipitated with mineral acid, and in both cases N-4-chloro-2-methylphenylmaleamido acid was isolated with m.p. 128-130° (identification by mixed melting point). Yield 84-86%.

Found M 237.42, 238.1. $C_{11}H_{10}O_3NCl$. Calculated M 239.6.

Reaction of N-p-methoxyphenylisomaleimide with hydrogen chloride. A 0.02-mole sample of N-p-methoxyphenylisomaleimide was dissolved in 40 ml of acetic acid and, without heating, hydrogen chloride was passed through the solution for 30 minutes. An orange precipitate which separated out was filtered, washed with ether, and dried.

Yield 63%. Crystallized from nitromethane, m.p. 158-159°. Found %: N 5.74. M 236.8. $C_{11}H_{10}O_3NCl$. Calculated %: N 5.85. M 239.5.

N-p-ethoxyphenylisomaleimide also reacted in a similar manner with hydrogen chloride, forming a salt with m.p. 164-165° in 68% yield.

Hydrolysis of the salt of N-p-methoxyphenylisomaleimide. A 0.0001-mole sample of the salt was heated to boiling with 15 ml of 1 N NaOH. To the cooled solution was added dilute mineral acid. The precipitate that separated out was filtered and dried. The compound which was obtained in 76% yield with m.p. 178-180° was N-p-methoxyphenylmaleamido acid (identified by mixed melting point). The salt of the isomaleimide was hydrolyzed rapidly even by cold water.

Conversion of the unsymmetrical N-arylmaleimides to the symmetrical isomers. A 0.015-mole sample of N-p-methoxyisomaleimide was mixed with the same amount of sodium acetate and 3 times the amount of acetic anhydride and heated on a boiling water bath for 30 minutes. The product was washed with ice water, filtered, and dried. N-p-Methoxyphenylmaleimide was obtained in 79% yield with m.p. 148-149°; a mixed sample with N-p-methoxyphenylmaleimide obtained previously directly from the corresponding acid, gave no depression in melting point.

SUMMARY

1. N-Arylmaleimides and N-arylisomaleimides have been prepared, and their structure has been demonstrated both by chemical methods and by means of infrared spectroscopy.

2. The N-arylisomaleimides are formed readily only in the case of arylamines containing substituents of the first group. In other cases it was not possible to obtain the isomaleimides.

3. The melting points of the isomaleimides that were synthesized were lower than those of the symmetrical imides.

4. The symmetrical maleimides were converted by the action of hydrogen chloride to α -chloro-N-arylsuccinimides.

5. The isomaleimides, in contrast to the symmetrical imides, reacted readily with hydrogen chloride to form at first colored salts in which the double bond $C = C$ was preserved, and then were converted to α -chlorosuccinimides.

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SYNTHESIS AND TRANSFORMATIONS OF (N-BENZOYLPYRROLIDON-2-YL-5)-ACETIC ACID

PREPARATION OF DERIVATIVES OF β -AMINOADIPIC ACID THROUGH THE β -CARBOXYL GROUP

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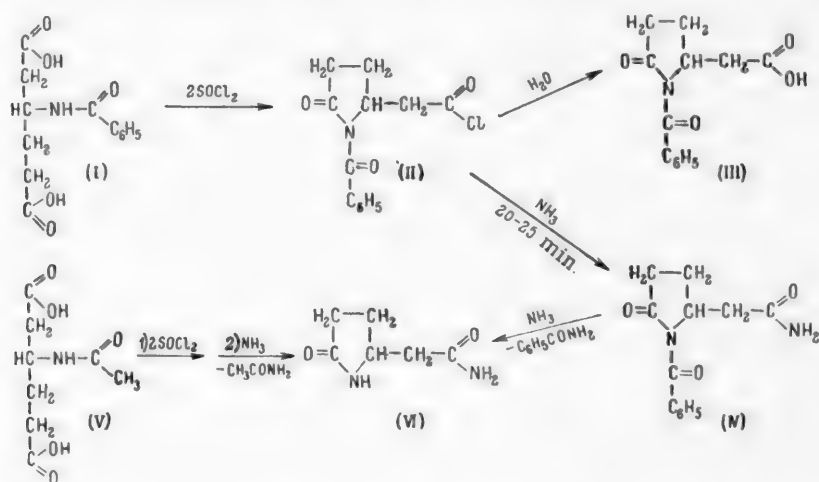
Methods for the synthesis of some difficultly available heterocyclic compounds have been developed by the school of V. M. Rodionov on the basis of various monocarboxylic β -amino acids [1].

In the present work we set up for ourselves the problem of finding a method for the preparation of monoamides or monohydrazides of dicarboxylic β -amino acids through the β -carboxyl group in the example of β -aminoadipic acid by way of hydrolytic cleavage of derivatives of (pyrrolidon-2-yl-5)-acetic acid (III).

It is known that it is possible to prepare N-tosyl- α -glutamine by the alkaline hydrolysis of the amide of (N-tosylpyrrolidon-2-yl-5)-carboxylic acid [2]. This synthesis was considerably simplified by Rudinger [3].

We established that when N-benzoyl- β -aminoadipic acid (I) is treated with thionyl chloride, the acid chloride of (N-benzoylpyrrolidon-2-yl-5)-acetic acid (II) is formed. Its structure was confirmed by a series of transformations. By slow hydrolysis of the acid chloride (II) in the air, (N-benzoylpyrrolidon-2-yl-1-5)-acetic acid (III) is formed. By the action of dry ammonia on the acid chloride (II) the amide (IV) is first formed in good yield and then goes over on more prolonged treatment to (pyrrolidon-2-yl-5)-acetamide (VI) with quantitative splitting off of the benzoyl group.

By reaction of N-acetyl- β -aminoadipic acid (V) with thionyl chloride and then with ammonia, (pyrrolidon-2-yl-5)-acetamide (VI) and acetamide are obtained. Splitting off of the acetyl group by the action of ammonia occurs so readily that even under mild conditions we did not succeed in isolating the N-acetylated lactam.



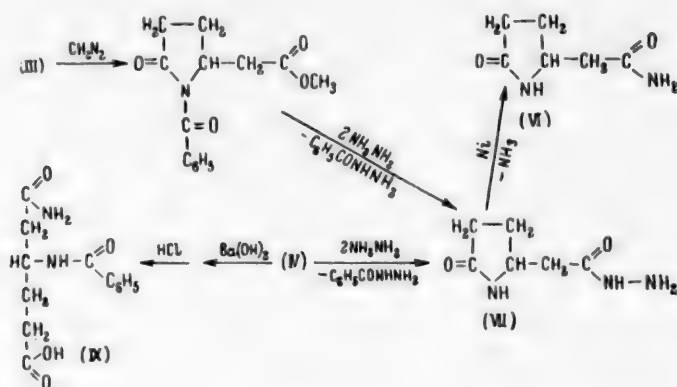
*In a preliminary communication [4] we suggested that on reaction of the N-acyl derivatives of β -aminoadipic acid with thionyl chloride, the diacid chlorides are first formed and their closure to lactams occurs under the influence of ammonia.

In connection with the fact that hydrolytic cleavage of the lactam in acid medium gives many byproducts [4], we decided to study in detail the action of some basic reagents.

When (N-benzoylpyrrolidon-2-yl-5)-acetamide (IV) is acted on by hydrazine, as also occurs when it is acted on by ammonia, splitting off of the benzoyl group takes place. As a result of this reaction the hydrazide of (pyrrolidon-2-yl-5)acetic acid (VII) and the hydrazide of benzoic acid were isolated in higher than 80% yield.

The structure of the hydrazide (VII) which was obtained was confirmed by its reverse synthesis. By the action of diazomethane on (N-benzoylpyrrolidon-2-yl-5)-acetic acid (III) its ester (VIII) was obtained, which was treated, without its being isolated, with hydrazine, whereupon we also noted the splitting off of the benzoyl group in the form of the hydrazide of benzoic acid and isolated a compound identical with the hydrazide (VII).

Furthermore, the hydrazide (VII) was characterized by its conversion to the amide (VI), which was previously known [5].



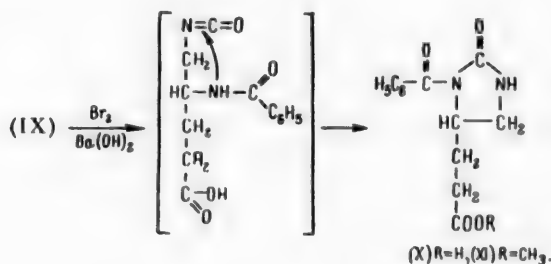
The hydrolytic cleavage of the lactam ring goes best, according to our observations, with a saturated solution of hydrated barium oxide.

As a result of the hydrolysis the β -amide of N-benzoyl- β -aminoadipic acid (IX) was obtained in 30-35% yield, identical with the compound previously prepared by us [4].

It is known that conversion to derivatives of glyoxalidone under the conditions of the Hofmann reaction is characteristic of amides of the N-acylated derivatives of β -aminoacids [6-8].

From the monoamide (IX) prepared by us we synthesized by the Hofmann reaction β -(3-benzoylglyoxalidonyl-4)-propionic acid (X), a biologically interesting analog of destiobiotin. The synthesis of the acid (X) was carried out under conditions similar to those used by Karrer and Schlosser [6]. It should be noted, however, that under our conditions we did not observe the splitting off of the benzoyl group.

The glyoxalidonylpropionic acid (X) that we isolated was converted by the action of diazomethane to the ester (XI).



EXPERIMENTAL

(N-Benzoylpyrrolidon-2-yl-5)-acetic acid (III). An 8.6-gram sample of N-benzoyl- β -aminoadipic acid (I) was mixed with 9 ml of thionyl chloride and left overnight. The precipitate that had formed was dissolved by shaking in anhydrous benzene. The benzene was distilled off in vacuum to dryness. This operation was repeated once again to remove the residual SOCl_2 and HCl . The acid chloride (II) was left in the air in a dish for 2-3 days, then triturated with 8-10 ml of cold water and filtered. Yield of acid (III) 7.4 g (92.5%), m.p. 130.5-131.5° (from water).

Found %: N 5.62, 5.69. $\text{C}_{13}\text{H}_{13}\text{O}_4\text{N}$. Calculated %: N 5.67.

(N-Benzoylpyrrolidon-2-yl-5)-acetamide (IV). As in the preceding experiment 12 g of N-benzoyl- β -aminoadipic acid (I) was treated with 11 ml of thionyl chloride. The precipitate of the acid chloride (II) after removal of the SOCl_2 and HCl was dissolved in anhydrous benzene and dry ammonia was passed into the solution for 20-25 minutes. The precipitate was quickly filtered off. If the reaction had gone to completion, additional saturation of the filtrate with ammonia did not lead to the formation of precipitate. The precipitate was carefully pressed out and washed twice with water. Yield of the amide (IV) 9.8 g (88%), m.p. 162.5-163° (from water).

Found %: C 63.13, 63.19; H 5.77, 5.70; N 11.34, 11.45. $\text{C}_{13}\text{H}_{14}\text{O}_3\text{N}_2$. Calculated %: C 63.47; H 5.74; N 11.39.

(Pyrrolidon-2-yl-5)-acetamide (VI). a) The precipitate of the acid chloride (II) from 3 g of the acid (I) was dissolved in a mixture of benzene and ether (1:1). Dry ammonia was passed for 1 hour through the solution, with cooling to 0-5°. The precipitate was filtered off and washed with water. The wash water was decolorized with the aid of activated carbon and evaporated to dryness. The precipitate was extracted with 99% alcohol. As the alcohol evaporated, crystals separated out from the alcoholic extract. Yield of amide (VI) 0.93 g (57.7%), m.p. 152-153° (from dioxane). According to the data of [5]: m. p. 149-150° (from ethyl acetate).

Found %: C 50.16, 50.22; H 7.34, 7.37; N 19.80, 19.61. $\text{C}_6\text{H}_{10}\text{O}_2\text{N}_2$. Calculated %: C 50.07; H 7.07; N 19.72.

The precipitate that did not dissolve in water was combined with the precipitate isolated after evaporation of the benzene filtrate and was recrystallized from water. This yielded 1.29 g (94.3%) of benzamide with m.p. 127°. A mixed sample with known benzamide gave no depression in melting point.

b) Six grams of N-acetyl- β -aminoadipic acid (V) was treated with 6 ml of thionyl chloride. After 6-8 hours 100 ml of anhydrous dioxane was added to the homogeneous mass and two thirds of the volume of the solvent was distilled off in vacuum. The residue was dissolved in 60 ml of absolute ether and dry ammonia was passed for 1.5 hours through the solution, cooled to +5°. The solution was filtered and the precipitate was washed twice with hot dioxane. A small precipitate of ammonium chloride remained on the filter. From the filtrate crystals of the amide (VI) precipitated after cooling. From the mother liquor after distilling off two thirds of the solvent an additional amount of the compound was obtained. Yield of amide (VI) 1.28 g (30.5%), m. p. 152-153° (from dioxane). A mixed sample with the compound obtained above gave no depression in melting point.

The mother liquor after isolation of the amide (VI) was diluted with ether, decolorized with carbon, and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuum the remaining oil crystallized. The crystals were separated on a porous plate. Yield 0.405 g (23%), m. p. 80.81° (from ethyl acetate). A mixed sample with known acetamide gave no lowering of the melting point.

Hydrazide of (pyrrolidon-2-yl-5)-acetic acid (VII). a) Three grams of (N-benzoylpyrrolidon-2-yl-5)-acetamide (IV) was mixed with 3 ml of anhydrous hydrazine. Noticeable heating occurred. After cooling, the reaction mass was extracted twice with ether, and then repeatedly with boiling benzene. The oil that did not dissolve in the benzene crystallized on cooling. Yield of hydrazide (VII) 0.64 g (33.5%), m. p. 157-158° (from dioxane).

Found %: N 27.10, 26.84. $\text{C}_6\text{H}_{11}\text{O}_2\text{N}_3$. Calculated %: N 26.77.

b) One-half gram of (N-benzoylpyrrolidon-2-yl-5)-acetic acid was mixed with 30 ml of absolute ether. To the suspension was added 15 ml of 1% diazomethane solution. The precipitate gradually dissolved. The solution was evaporated, 0.5 ml of hydrazine was added to the oil that was obtained, and the mixture was heated for 1 hour on a boiling water bath, then the hydrazide (VII) was isolated as described above. Yield 0.17 g (53.5%), m. p. 158-158.5° (from dioxane).

From the ethereal and benzene extracts the hydrazide of benzoic acid was isolated.

Reaction of the hydrazide (VII) with Raney nickel. By stirring and heating 1 g of hydrazide (VII) was dissolved in 60 ml of alcohol, and without discontinuation of the stirring 20 g of Raney nickel was introduced into the solution, which was brought to boiling. The heating and stirring were continued until the evolution of ammonia ceased (litmus test). The hot solution was filtered and evaporated in vacuum. Yield of amide (VI) 0.63 g (69.6%), m. p. 150-152° (from dioxane). A mixed sample with (pyrrolidon-2-yl-5)-acetamide (VI) obtained above gave no lowering of the melting point.

β -Amido-N-benzoyl- β -aminoadipic acid (IX). Five grams of amide (IV) was stirred into 60 ml of water. To suspension there was added dropwise, with stirring, a saturated solution of hydrated barium oxide until an almost clear solution was produced. The solution was filtered and acidified with hydrochloric acid (d 1.18) to an acid reaction to congo and then left for 1 hour at 0-5°. The precipitate that had settled out was filtered off, washed with water, and several times with ether to remove benzoic acid. Yield of amide (IX) 1.95 g (36.5%), m. p. 249-249.5° (from water).

Found %: N 10.43, 10.39. M 213.2. $C_{13}H_{16}O_4N_2$. Calculated %: N 10.60. M 212.0.

From the ether solution 1.25 g (50%) of benzoic acid was recovered.

β -(3-N-Benzoylglyoxalidonyl-4)-propionic acid (X). A mixture of 3.2 g of amide (IX), 28 ml of a solution of 15 g of $Ba(OH)_2 \cdot 8H_2O$ in 300 ml of water, 0.6 ml of bromine, and 50 ml of water was prepared. The reaction mixture was shaken vigorously until a white flocculent precipitate formed. After this 112 ml of $Ba(OH)_2$ solution of the same concentration was added, whereupon the precipitate completely dissolved. After 25 minutes the flask was placed for 1 hour in a water bath heated to 90°, then the solution was cooled to room temperature and carefully acidified with 10% H_2SO_4 solution to remove barium ions. After separation of the $BaSO_4$ the filtrate was transferred to a conical flask, protected from the light, 4.1 g of Ag_2CO_3 was added, and the reaction mass was stirred for 2-3 hours. The precipitate was removed and the filtrate was concentrated in vacuum at a temperature not higher than 39°. Yield of acid (X) 0.55 g (17.3%), m. p. 180-180.5° (from water).

Found %: C 59.75, 59.78; H 5.81, 5.63; N 10.88, 10.97. $C_{13}H_{14}O_4N_2$. Calculated %: C 59.53; H 5.38; N 10.68.

Methyl ester of β -(3-N-benzoylglyoxalidonyl-4)-propionic acid (XI). To a mixture of 0.15 g of (X) in 20 ml of ether was added a 2-fold excess of an ether solution of diazomethane. After an hours stirring the precipitate was removed from the ether, washed, and dried. Yield of ester (XI) 0.124 g (76%), m. p. 159.5-160.5° (from water).

Found %: C 60.64, 60.65; H 6.01, 6.10; N 10.03, 10.14. $C_{14}H_{16}O_4N_2$. Calculated %: C 60.92; H 5.48; N 10.15.

SUMMARY

1. It has been found that the reaction of N-benzoyl- β -aminoadipic acid with thionyl chloride produces the acid chloride of (N-benzoylpyrrolidon-2-yl-5)-acetic acid, the starting material for the synthesis of derivatives of (pyrrolidon-2-yl-5)-acetic acid and of β -aminoadipic acid through the β -carboxyl group.

2. A Hofmann reaction was carried out with N-benzoyl- β -aminodadipic acid and β -(2-N-benzoylglyoxalidonyl-4)-propionic acid was obtained.

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THE ABSORPTION SPECTRA AND STRUCTURES OF GLUTACONIC ALDEHYDE DIANILS

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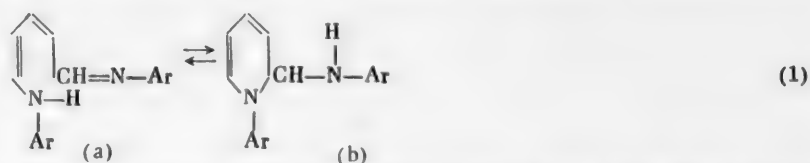
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Like other nonsalt-forming compounds, the so called inner ionoid compounds, glutaconic aldehyde dianils are sensitive to the nature of the solvent. Like the monoanils of glutaconic aldehyde [4], the dianils give deeply colored salts with acids and alkalis, and it can be assumed that the amphoteric substances are involved in tautomeric changes.



König suggested such tautomerism in salts of glutaconic aldehyde dianils (pyridine dyes), with which he connected changes in color of the crystals obtained from different solvents [5]. Zincke [6] denied this idea, explaining the change in color of the dye crystals by dimorphism. The double nature of the glutaconic aldehyde dianils was indirectly shown in several chemical transformations [7]; special studies of the tautomerism of glutaconic aldehyde dianils and thier salts have not been made.

We have studied the absorption spectra of glutaconic aldehyde dianils in different solvents and have found that in solvents with low dielectric permeability [8,9], dichloroethane or benzene, the color disappears on short standing; determination of the spectra with time leads us to believe that in these solvents there is a shift in equilibrium of the tautomeric form (1).

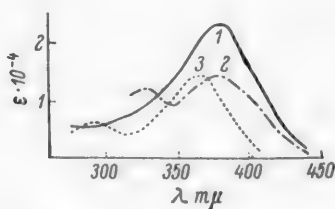


Fig. 1. Absorption spectra of solutions of dianil (I) in benzene. 1) freshly prepared solution; 2) after one hour; 3) solution after a day.

From comparison of the results in Table 1 we see that the structure of the aromatic radicals has a notable effect on change in the absorption spectra in a single solvent and on the size of shift of γ_{\max} of the chief absorption band in different solvents.

The change in absorption spectra of dianils (I) and (II) in benzene with time is shown in Figs. 1 and 2. It was interesting to follow the character of change in spectrum of dianil (III) in a mixture of benzene with butanol, since

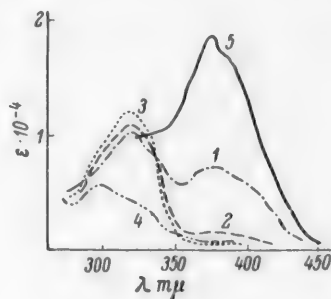


Fig. 2. Absorption spectra of dianil (II) in benzene. 1) freshly prepared solution; 2) solution after 30 min.; 3) solution after 2 hours; 4) solution after a day; 5) freshly prepared solution measured from 320 mμ.

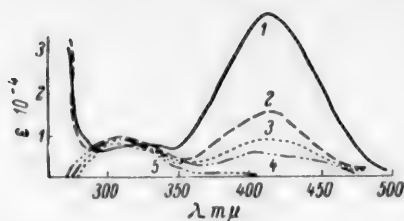


Fig. 3. Absorption spectra of dianil (III) in benzene-butanol mixtures; 1) in a mixture of benzene-butanol (20:80); the dianil was dissolved in butanol, then the solution was diluted with benzene; 2) the same solution after two hours; 3) in a mixture of benzene-butanol (20:80); the dianil was dissolved in benzene; 4) the same solution after two hours; 5) the same solution after a day.

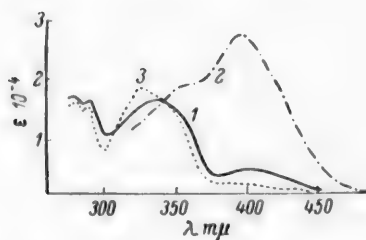


Fig. 5. Absorption spectra of dianil (VIII) solutions in benzene. 1) freshly prepared solution, measured from 275 mμ; 2) freshly prepared solution, measured from 320 mμ; 3) the same solution after 30 min. measured from 275 mμ.

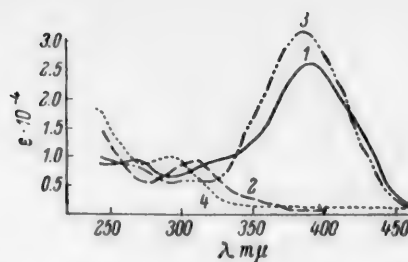


Fig. 4. Absorption spectra of solutions of dianils (II) and (III) in dichloroethane. 1) freshly prepared solution of dianil (III); 2) the same solution after a day; 3) freshly prepared solution of dianil (II); 4) the same solution after a day.

the solutions of dianil in butanol were considerably more stable (Fig. 3). The character of the absorption spectra in prepared mixtures of benzene and butanol was the same as in the case when the dianil was dissolved in the benzene first; in both cases there at once appeared in the spectrum an absorption band with a maximum at 319 mμ, while on solution of the dianil in butanol and later dilution with benzene of the dianil (III), a clear band in this region appeared after several minutes.

Change of dianils (II) and (III) occurs more slowly in dichloroethane (Fig. 4). Benzene solutions of dianil (VIII) change at a greater rate with time (Fig. 5).

The appearance of the absorption curves obtained with time from solutions of dianils in benzene of the same concentrations (Figs. 1-3,5) are given; the appearance of the isobathic point, though not always clear, suggests that in benzene solutions there occurs a shift in tautomeric equilibrium toward form (b).

The band at the edge of the visible region evidently depends on form (a).

In alcohols and in the crystalline state, due to the formation of hydrogen bonds, form (a) is probably stabilized. The reverse transformation of form (b) into form (a) under the conditions of the experiment was not found. It is known that the reciprocal conversions of tautomeric forms do not always occur, even in typical tautomeric compounds [10, 11].

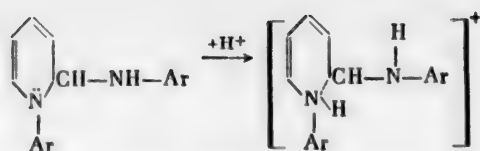
The different colors of acid and alkaline salts of analogous structure (Table 2) are connected with tautomeric conversions of glutaconic aldehyde anils. The acid salts of glutaconic aldehyde dianils are easily obtained in the crystalline state (pyridine dyes); the alkaline salts can exist only in solution; they are formed in pyridine in the presence of sodium amide [12] or in acetone with an excess of anhydrous potassium hydroxide [13].

As Table 2 shows, all the anions are more deeply colored than the corresponding cations. In an acid medium the dianils have comparatively strong basic properties which are inherent in form (b). In forming the cation the bond C-N is partly polarized and the degree of its polarization depends on the nature of the radical on the nitrogen atom. Polarization of the C-N bond, which increases the conjugation, leads along with ionization of the molecule to a considerable bathochromic effect.

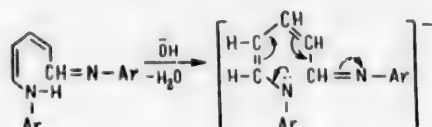
TABLE 1. Effect of Nature of Solvent on Absorption Spectra of Glutaconic Aldehyde Dianils

No.	Glutaconic aldehyde dianil, amine derivative	M. p.	Appearance of crystals (solvent for crystallization)	Empirical formula	% N		$\lambda_{\max} (\epsilon \cdot 10^{-4})$				
					found	calc.	solvent				
							methanol	ethanol	butanol	acetone	dichloroethane
I	Aniline	85—86°	Brown (methanol with water)	$C_{17}H_{16}N_2$	11.43	11.29	260 (0.8) 403 (5.1)	250 (0.9) 406 (6.5)	— 410 (5.3)	— 388 (4.6)	270 (0.8) 383 (3.9)
II	p-Toluidine	111—112	Dark brown (methanol with water)	$C_{19}H_{20}N_2$	10.10	10.15	260 (1.5) 410 (5.3)	260 (1.7) 412 (3.4)	255 (1.3) 415 (4.3)	— 395 (3.3)	— 378 (2.9)
III	p-Anisidine	72—73	Orange (methanol with water)	$C_{19}H_{20}O_2N_2$	9.26	9.09	255 (2.1) 300 (1.2) 420 (4.5)	258 (2.5) 300 (1.6) 415 (3.9)	260 (4.4) — 420 (2.6)	— 325 (3.2) 395 (2.5)	— 318 (1.7) 382 (2.2)
IV	p-Dimethylaminoaniline	110	Dark brown (acetone with methanol)	$C_{21}H_{26}N_4$	16.73	16.76	258 (1.7) 407 (1.4)	255 (1.6) 440 (3.4)	— —	— 425 (1.3)	310 (1.4) 426 (2.6)
V	Ethyl p-amino-benzoate	165	Brown (methanol with water)	$C_{21}H_{24}O_4N_2$	7.04	7.14	298 (1.7) 345 (1.6) 420 (2.7)	298 (2.2) — 422 (5.1)	250 (1.3) 300 (1.7) 425 (2.7)	— — 405 (2.1)	— 280 (2.9) 340 (1.2)
VI	p-Nitroaniline	107	Black (methanol with water)	$C_{17}H_{14}O_4N_4$	16.51	16.52	— —	215 445	— —	380 (1.5) 442 (2.5)	355 385
VII	α -Naphthylamine	93	Orange (methanol with water)	$C_{23}H_{20}N_2$	8.07	8.05	— 413 (4.7)	337 (0.8) 417 (3.8)	337 (0.8) 417 (3.9)	— 405 (3.6)	338 (0.9) 400 (2.3)
VIII	β -Naphthylamine	90	Orange (methanol)	$C_{23}H_{20}N_2$	8.08	8.05	290 (1.77) 422 (5.2)	290 (1.5) 425 (5.6)	290 (1.4) 430 (4.4)	— 405 (9.2)	290 (1.6) 330 (1.6) 395 (2.8)

• The dianil did not fully dissolve



In alkaline solution, the dianils behave like weak acids; the equilibrium of the tautomeric forms is shifted to the side of (a). Formation of the anion is accompanied by splitting of a proton from the nitrogen atom. Equalization of the bonds (due to the presence of the conjugated chain) and ionization of the molecule produce a greater bathochromic effect than occurs with the corresponding cation.



Steric hindrance is absent in the anion which permits salts of the dianils in some acids. Thus, in the cation of the α -naphthylamine derivative as compared to the β -isomer, the absorption maximum is shifted hypsochromically by 30 m μ , which is caused by spacial hindrance inherent in many α -substituted naphthalenes [14], while the difference in position of the absorption maximum of the corresponding anions is 10 m μ (see Table 2).

TABLE 2. Long Wave Absorption Maxima (m μ) of Anions (−) and Cations (+) of Glutaconic Aldehyde Dianils

Aniline		p-Anisidine		α -Naphthyl-amine		β -Naphthyl-amine		p-Nitroaniline	
(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
485	505	500	515	480	535	510	545	530	690

The literature results do not permit finding definite regularities in change of color of cations and anions of analogous structures. The facts are known when the corresponding cations and anions have similar spectra [15]; some authors [15,16] consider that the character of the charge of the ion does not affect the position of the absorption bands of the corresponding cations and anions. A case is known of a considerable deepening of color of anion as compared to the color of the analogous cation [12]. However, sometimes, even among dyes of the same class there is no definite dependence of change of color of cation and anion of analogous structures [17].

A comparison of the absorption spectra of glutaconic aldehyde dianils in different solvents convinces us that the solvatochromic properties of the bases depends preferably on tautomeric changes which depend on the nature of the solvent and the structure of the dianil.

EXPERIMENTAL

Glutaconic aldehyde dianils were purified by reprecipitation from methanol by water and sometimes were crystallized from methyl alcohol. The purified preparations were kept over sulfuric acid in a desiccator. The solvents for determination of the absorption spectra were dehydrated and fractionated. The cryoscopic benzene was dried over calcium chloride and fractionated. Dichloroethane, dried over sodium sulfate, was used only when freshly prepared. The alcohols were fractionated over alkali without preliminary drying.

The absorption spectra of the glutaconic aldehyde dianils were measured on an SF-4 spectrophotometer. The concentration of alcohol and acetone solutions was $1 \cdot 10^{-5}$ M, of the solutions in dichloroethane and benzene, $2 \cdot 10^{-5}$ M, in the mixture of benzene-butanol, $1,5 \cdot 10^{-5}$ M. Dianil (VI) was difficultly soluble in organic solvents except acetone; its spectrum was determined qualitatively.

The solution of alkali salts were obtained by energetic shaking of acetone solutions of the glutaconic aldehyde dianils with dry sodium hydroxide, pieces of which remained at the bottom of the cuvette during the measurement. The absorption spectra of the dianil salts was determined on an SF-2M spectrophotometer.

SUMMARY

1. We have studied the absorption spectra of seven glutaconic aldehyde dianils in several solvents. We have compared the spectra of acid and alkali salts of five dianils in acetone.

2. We have suggested that the solvatochromic effect in glutaconic aldehyde dianils is caused by tautomeric transformations.

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STUDIES IN THE SERIES OF ALKYLATED AMINES OF THE AROMATIC SERIES

V. PREPARATION OF PRIMARY-QUATERNARY ALKYLATED DERIVATIVES OF *p*-PHENYLENEDIAMINE

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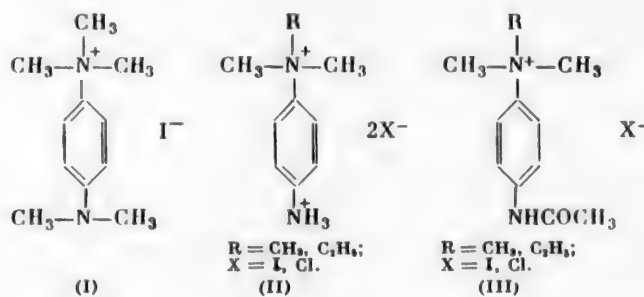
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 8,

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Interest in alkylated derivatives of *p*-phenylenediamine has been aroused in pharmacology and synthetic chemistry because trimethyl-(*p*-dimethylaminophenyl)-ammonium iodide (I) has shown ephedrine-like properties, especially in its ability to raise the blood pressure [1,2]. In order to study the relation between pharmacological action and chemical structure of substances, it was of interest to synthesize compounds similar in structure to this amine (I), but containing in the para-position to the quaternary ammonium group a primary or secondary amine group.

In the present work we describe the preparation of the iodide and chloride of a primary-quaternary derivative of *p*-phenylenediamine with the structure (II).



N,N,N-Trimethyl-*p*-phenylene bisammonium dichloride (II, R = CH₃, X = Cl) was described in the literature [3] and has been used as a diazo compound for basic azo dyes [4]. N, N, N-Trimethyl-*p*-phenylene bisammonium diiodide (II, R = CH₃, X = I) and also N, N, N-dimethylethyl *p*-phenylene bisammonium dichloride (II, R = C₂H₅, X = Cl) and diiodide (II, R = C₂H₅, X = I) have not been described in the literature and were obtained for the first time by us.

For the synthesis of these substances we started from *p*-aminodimethylaniline. Its acetyl derivative easily added alkyl iodide with the formation of dimethylalkyl-*p*-(acetaminophenyl)-ammonium iodide (III, R = CH₃, C₂H₅; X = I), which on hydrolysis by acids formed the diiodide or dichloride of N, N, N-dimethylalkyl-*p*-phenylene bisammonium (II, R = CH₃, C₂H₅; X = I, Cl); in the latter case it was necessary first to change the iodide into the chloride.

The acetylation of *p*-aminodimethylaniline has often been mentioned in the literature [5-8]. However, none of these reports gives a sufficiently detailed method of synthesis. The conditions which we have taken for acetylation of *p*-aminodimethylaniline in glacial acetic acid with the calculated amount of acetic anhydride assure a sufficiently high yield of product (49.3% after crystallization) and exclude the formation of *p*-diacetaminodimethylaniline. The iodoalkylation of *p*-acetaminodimethylaniline was carried out in anhydrous acetone with heating. Iodomethylation of this compound had already been described [3,7]. The first authors carried out the reaction in benzene with heating under pressure; the second, at room temperature in the course of several days. The authors did not give the yield of product and only in paper [3] was given the m.p. 226° and some properties of the compound. According

to our results, trimethyl-(*p*-acetylaminophenyl)-ammonium iodide (III, R = CH₃, X = I) has m. p. 230-231 °* and the yield was 84.3-87.7%.

Hydrolysis of the acetyl derivatives of the iodoalkylates was carried out by boiling the substances with dilute hydriodic acid which did not contain iodine. The iodides of the primary-quaternary *p*-phenylenediamines (II, R = CH₃, C₂H₅; X = I) were colorless and well crystallized. However, with time they took on a yellow color due to evolution of iodine. The N, N, N-dimethylethyl-*p*-phenylene bisammonium diiodide was especially unstable and turned yellow in the course of one to two weeks.

The dimethylalkyl-(*p*-acetylaminophenyl)-ammonium iodides (III, R = CH₃, C₂H₅; X = I) were changed to the chlorides by reaction with moist, freshly precipitated silver chloride in water. The dimethylalkyl-(*p*-acetylaminophenyl)-ammonium chlorides were isolated from the water solution in the form of crystal hydrates which lost water only by energetic drying at 115°. Hydrolysis of the chlorides into primary-quaternary *p*-phenylenediamine derivatives was carried out by boiling with 4 N hydrochloric acid. The salts were isolated in the form of very stable, colorless crystals. Of these, trimethyl-*p*-aminophenyl ammonium chloride (II, R = CH₃, X = Cl) had been previously obtained [3].

Both N, N, N-dimethylalkyl-*p*-phenylene bisammonium diiodides and dichlorides (II) were titrated with alkali in water solution and formed with *p*-dimethylaminobenzaldehyde light red orange azomethines.

A pharmacological study of the primary-quaternary *p*-phenylenediamine derivatives, carried out by Yu. I. Lisunkin, showed that replacement of the alkyl radical in the tertiary amine group of (I) by hydrogen (II) led to disappearance of the pressor action in these compounds.

EXPERIMENTAL

D-Acetylaminodimethylaniline. We dissolved 50.35 g of freshly distilled *p*-aminodimethylaniline in 110 ml of glacial acetic acid and added 38 ml of acetic anhydride. The reaction mixture was boiled for one hour and evaporated as completely as possible in a vacuum. The residual brown oil crystallized on cooling (weight 70 g). It was crystallized from 600 ml of water with charcoal. A grayish product with m.p. 131-132° precipitated (25.45 g). Addition of a 10% solution of sodium hydroxide (to phenolphthalein) to the filtrate, precipitated a further 20.15 g of the same substance with m.p. 131-132°. In all we obtained 45.60 g (69.1%). After repeated crystallization from water (20 ml for each gram of substance) with charcoal we obtained 32.4 g (49.3%) of a colorless, crystalline product with m.p. 135-137°. The literature gives 132-133°.

Alkylation of *p*-acetylaminodimethylaniline. On mixing and heating 0.1 mole of *p*-acetylaminodimethylaniline it dissolved in 90 ml of anhydrous acetone. Then we added 130% of the alkylating agent (methyl iodide or ethyl iodide). Almost immediately a precipitate of the quaternary derivative separated. The reaction mixture was heated with stirring on a boiling water bath for ten minutes for iodomethylation and 2-2.5 hours for iodoethylation. On the next day the precipitate was filtered off and washed with anhydrous acetone. The yield of methylation product was 90.8-99.4%, and the iodoethylation product yield was 73.4-78.3%. For final purification the substances were crystallized from the corresponding solvent (Table 1).

Conversion of the iodoalkylates of *p*-acetylaminodimethylaniline into the chloroalkylates. We dissolved 0.1 mole of the iodoalkylate of *p*-acetylaminodimethylaniline in 300 ml of water at 40-60° and added to the solution 200% of freshly precipitated silver chloride, carefully washed free from hydrochloric acid. The mass was stirred energetically for 8-12 hours at room temperature. The silver salt was filtered from the mixture, the filtrate was boiled with charcoal and evaporated dry in a vacuum. The yield of chloroalkylate hydrates was almost quantitative. For freeing the products from water they were dried at 115° (Table 1).

Hydrolysis of the iodoalkylates of the acetyl derivatives. We boiled for 2.5 hours a mixture of 0.01 mole of iodoalkylate of *p*-acetylaminodimethylaniline, 20 ml of freshly prepared concentrated hydriodic acid, free from iodine, (d 1.553), and 40 ml of water. The solution was evaporated in a vacuum to 1/5-1/10 the original volume. The yellowish precipitate was filtered and dried. Yield quantitative. For final purification the substances were crystallized from alcohol (Table 2).

Hydrolysis of the chloroalkylates of the acetyl derivatives. We boiled for 1.5 hours a mixture of 0.01 mole of the chloroalkylate of *p*-acetylaminodimethylaniline and 240 ml of 4 N hydrochloric acid, treated it with charcoal, filtered, and evaporated dry in a vacuum. Colorless crystalline precipitate. Yield quantitative. For purification it was crystallized from alcohol (Table 2).

*In two experiments we obtained the same compound in analytically pure state with m. p. 257.5°. We have found no explanation of this effect.

TABLE 1. Dimethylalkyl-(p-acetylamino-phenyl)-ammonium halides



Compound	RX	Empirical formula	Solvent for crystallization	Yield after crystallization, %	M. p. °	Found, %			Calculated, %		
						N	X	H ₂ O**	N	X	H ₂ O
Trimethyl-(p-acetylaminophenyl)-ammonium iodide	CH ₃ I	C ₁₁ H ₁₇ ON ₂ I	Methanol	83.4—87.7	230—231°***	8.67, 8.77	39.65, 39.71	—	8.75	39.64	—
Dimethylethyl-(p-acetylaminophenyl)-ammonium iodide	C ₂ H ₅ I	C ₁₂ H ₁₉ ON ₂ I	Anhydrous alcohol	65.8—66.8	196—198	8.49, 8.40	38.13, 36.15	—	8.38	37.98	—
Trimethyl-(p-acetylaminophenyl)-ammonium chloride	CH ₃ Cl	C ₁₁ H ₁₇ ON ₂ Cl	—	—	240°*** (Sublimate)	12.57	15.48, 15.54	—	12.25	15.50	—
The same, crystal hydrate	CH ₃ Cl	C ₁₁ H ₁₇ ON ₂ Cl · H ₂ O	Anhydrous alcohol	75.8	The same	11.51, 11.44	14.07, 14.18	7.74, 7.73	11.36	14.37	7.30
Dimethylethyl-(p-acetylaminophenyl)-ammonium chloride	C ₂ H ₅ Cl	C ₁₂ H ₁₉ ON ₂ Cl	—	—	210—211	11.35, 11.35	14.57, 14.51	—	11.54	14.61	—
The same, crystal hydrate	C ₂ H ₅ Cl	C ₁₂ H ₁₉ ON ₂ Cl · 1/2 H ₂ O	Precipitated from anhydrous alcohol by absolute ether or crystallized from a mixture of anhydrous alcohol and benzene	93.7	The same	10.83, 10.70	13.87, 13.91	3.68, 3.69	11.13	14.08	3.58

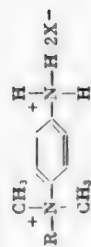
* M. p. determined on a Hoffer block.

** Water of crystallization.

*** The literature [3] gives m. p. 226°.

**** It is interesting to note that the prismatic crystals of the crystal hydrate of trimethyl-(p-acetylaminophenyl)-ammonium chloride before melting at 220° are converted into rhombs, which sublime at 240°.

TABLE 2. N,N,N-Dimethylalkyl-p-phenylene bisammonium halides.



Compound	R	X	Empirical formula	Solvent for crystallization	Yield after crystallization, %	M. p.	Found, %		Calculated, %	
							N	X	N	X
N,N,N-Trimethyl-p-phenylene bisammonium diiodide	CH ₃	I	C ₉ H ₁₈ N ₂ I ₂	Aqueous alcohol (5:1)	53.7—60.4	228—230°	7.04, 7.04	62.94, 62.93	6.90	62.51
N,N,N-Dimethylethyl-p-phenylene bisammonium diiodide	C ₂ H ₅	I	C ₁₀ H ₁₈ N ₂ I ₂	Alcohol	67.4	196—198	6.85, 6.61	60.82, 60.92	6.67	60.42
N,N,N'-Trimethyl-p-phenylene bisammonium dichloride	CH ₃	Cl	C ₉ H ₁₈ N ₂ Cl ₂	Alcohol	69.4—74.1	218*	12.71, 12.63	31.54, 31.41	12.56	31.78
N,N,N-Dimethylethyl-p-phenylene bisammonium dichloride	C ₂ H ₅	Cl	C ₁₀ H ₁₈ N ₂ Cl ₂	Alcohol	59.7—83.7	218° (slow heating); 232° (rapid heating)	11.93, 11.86	30.40, 30.22	11.81	29.90

* According to the literature, m.p. 219° [3].

SUMMARY

1. We have studied the iodomethylation and iodoethylation of p-acetylamino-dimethylaniline.
2. We have obtained N, N, N-trimethyl- and N, N, N-dimethylethyl-p-phenylene bisammonium diiodide and dichloride.

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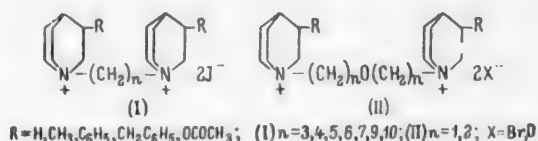
THE SYNTHESIS OF POLYMETHYLENE-BIS-QUINUCLIDINEUM HALIDES

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Biological study of symmetrical and unsymmetrical diquaternary salts of pyridine, piperidine, quinoline, α - and β -carboline, and other nitrogen-containing cyclic systems has shown that the nature of the action of such compounds is determined by the cyclic system which participates in formation of the quaternary salt and by the length of the carbon chain between the quaternary nitrogen atoms [1-5].

Compounds of analogous type which have as the nitrogen-containing heterocycle quinuclidine were not studied until recently, and only in 1960 appeared a patent report on the synthesis and properties of unsymmetrical quaternary salts, in whose composition appeared this heterocycle [6].

In the present work we describe the synthesis of symmetrical diquaternary salts: polymethylene-bis-quinuclidinium halides (I) and (II).



The quinuclidine needed for the synthesis of compounds (I) and (II) could be obtained by cyclization of 4-(β -haloethyl)-piperidine [7,8] by heating 3-(β -bromoethyl)-1,5-dibromopentane with ammonia [9,10], or by reduction of 3-bromo(chloro)-quinuclidine, dehydroquinuclidine [11], or 3-quinuclidone [12].

Each of these methods had one or more deficiencies which prevented its use for the synthesis of large amounts of quinuclidine.

The greatest deficiency, which was characteristic of almost all the methods known for obtaining quinuclidine was the many stage synthesis of the starting substances, sometimes giving small yields. Of the above mentioned compounds the most suitable at the present time is 3-quinuclidone. It is known that on heating the oily hydrazone of 3-quinuclidone with sodium ethylate at 175° quinuclidine is formed [12]. However, quinuclidine was isolated only in the form of the picrate, whose yield was not given.

We have obtained a crystalline hydrazone of 3-quinuclidone and treated it according to Clemo and Metcalf. The yield of quinuclidine was 52%. It was necessary to carry out the reaction under pressure which made it difficult to obtain larger amounts of quinuclidine by this method.

As our study showed, the best process for getting quinuclidone according to Kischner by direct heating of the ketone with hydrazine hydrate and potassium hydroxide in glycerol solution. The yield of quinuclidine was then almost quantitative.

3-Substituted quinuclidines were obtained by the method described in our previous work [13].

α, ω -Diiodoalkanes were synthesized from the corresponding glycols through the dichloro derivatives by the action of sodium iodide. This path was available for the synthesis of substances in which n = from 3 to 7, 9, and 10.

The reaction of quinuclidine and its 3-substituted derivatives with α, ω -diiodoalkanes was carried out by heating two equivalents of the base with one mole of dihalogen compound in alcohol or acetone solution. Acetone was used as the solvent in obtaining derivatives of 3-acetoxyquinuclidine. The diquaternary salts were purified by recrystallization from methanol, ethanol, a mixture of these two alcohols, or a mixture of ethanol with acetone.

The results of the biological studies of these diquaternary salts will be published later.

EXPERIMENTAL

3-Quinuclidone hydrazone. We boiled 4 g of sublimed 3-quinuclidone and 12 ml of 70% hydrazine hydrate for 40 hours. The reaction mass was filtered from turbidity, evaporated in a vacuum, and gave a thick mass which was carefully dried by repeated addition of anhydrous benzene, followed by distilling it off. We obtained 4 g (90%) of a crystalline hydrazone of 3-quinuclidone. Colorless platelets, easily soluble in water, alcohol, acetone, benzene, insoluble in ether. M.p. 87-90° (from a mixture of benzene and ether).

Found %: C 60.29; H 9.51; N 30.25. $C_7H_{13}N_3$. Calculated %: C 60.43; H 9.35; N 30.21.

Quinuclidine. Ten g of 3-quinuclidone, 15 ml of hydrazine hydrate, 15 g of potassium hydroxide, and 100 ml of glycerol were heated under reflux for four hours at 165-175°, then the quinuclidine was distilled with water, gradually raising the temperature of the bath to 270°. The distillate was extracted with ether, the ether solution was dried with potash and evaporated to give 8.7 g (97.5%) of quinuclidine in the form of clear, volatile crystals with m.p. 154° [7].

Picrate m. p. 272-273° (from alcohol)

Found %: C 45.79; H 4.74; N 16.07. $C_7H_{13}N \cdot C_6H_5O_7N_3$. Calculated %: C 45.88; H 4.70; N 16.47.

Ethiodide m. p. 291-293° (from a mixture of alcohol and ether).

Found %: N 5.17; J 47.50. $C_9H_{18}NJ$. Calculated %: N 5.24; J 47.56.

3-Benzyl-1-azabicyclo-(2,2,2)-2-octene. We converted 29.7 g of 3-benzyl-3-hydroxyquinuclidine [13] into the hydrochloride which was mixed with 175 ml of thionyl chloride and 300 ml of anhydrous benzene; the mixture was heated on a water bath for three hours at 40-50° and for six hours with boiling. The benzene and thionyl chloride were distilled off in a vacuum, the residue was made alkaline with a 50% potash solution, and the alkaline solution was extracted with chloroform. After removal of the chloroform the residue was mixed with a solution of 7.8 g of potassium hydroxide in 90 ml of anhydrous alcohol and boiled for six hours. The precipitate of potassium chloride was filtered off, the alcohol solution was acidified with hydrochloric acid, evaporated in a vacuum, the residue was treated with a 50% potash solution, and extracted with ether. From the ether solution we obtained 20 g (73.3%) of 3-benzyl-1-azabicyclo-(2,2,2)-2-octene. B. P. 118-121° (0.8 mm). Colorless, mobile liquid easily soluble in organic solvents.

Hydrochloride m. p. 190-193° (from a mixture of alcohol and ether).

Found %: N 5.96; Cl 14.98. $C_{14}H_{17}N \cdot HCl$. Calculated %: N 5.94; Cl 15.08.

3-Benzylquinuclidine. 3-Benzyl-1-azabicyclo-(2,2,2)-2-octene hydrochloride obtained from 18.9 g of the base was reduced in a solution of 200 ml of anhydrous alcohol in the presence of 0.7 g of platinum oxide. After absorption of one mole of hydrogen, the platinum black was filtered off, the alcohol solution was evaporated in a vacuum, and in the usual way we isolated from the residue the base 3-benzylquinuclidine. Yield 17.5 g (90%). The substance was a colorless, mobile liquid, easily soluble in water and organic solvents. B. p. 103-105° (0.3 mm).

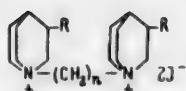
Hydrochloride, colorless crystalline powder with m. p. 198-199°.

Found %: N 5.99; Cl 14.85. $C_{14}H_{19}N \cdot HCl$. Calculated %: N 5.88; Cl 14.94.

1,7-Dichloroheptane. To 19 g of 1,7-dihydroxyheptane we added with cooling and stirring 55 g of thionyl chloride. After mixing the reagents, stirring was continued for two hours more, then the mixture was evaporated and the residue was distilled. The resulting substance was washed with water, with a water solution of sodium bicarbonate, again with water, was dried with sodium sulfate, and distilled. Yield 20.57 g (89.5%). B. p. 106-107° (13 mm) [14].

1,7-Diiodoheptane. We boiled 20.57 g of 1,7-dichloroheptane, 73 g of sodium iodide, and 300 ml of dry acetone for 26 hours. The reaction mass was filtered from the inorganic salt, evaporated in a vacuum, the residue dissolved in ether, the ether solution washed with water and dried with sodium sulfate. After distillation of the ether the substance was distilled in a vacuum. B. P. 160° (14 mm) [15]. Yield 32.7 g (78%).

TABLE 1.



R	n	Yield %	M.p.	Empirical formula	% N		% J	
					Found	Calc.	Found	Calc.
H	3	66.0	277—278°	C ₁₇ H ₃₂ N ₂ I ₂	5.35	5.41	48.98	49.03
H	4	81.0	290	C ₁₈ H ₃₄ N ₂ I ₂	—	—	47.57	47.74
H	5	64.0	265—266	C ₁₉ H ₃₆ N ₂ I ₂	5.09	5.12	46.50	46.52
H	6	78.0	247—249	C ₂₀ H ₃₈ N ₂ I ₂ · H ₂ O	4.61	4.83	43.92	43.94
H	7	76.0	211—213	C ₂₁ H ₄₀ N ₂ I ₂ · H ₂ O	4.57	4.73	—	—
H	9	66.5	237	C ₂₃ H ₄₄ N ₂ I ₂	4.97	4.65	—	—
H	10	75.8	277—278	C ₂₄ H ₄₆ N ₂ I ₂	4.47	4.54	41.15	41.20
CH ₃	3	89.0	263—264	C ₁₉ H ₃₆ N ₂ I ₂ · H ₂ O	—	—	45.06	45.07
CH ₃	4	91.2	271—273	C ₂₀ H ₃₈ N ₂ I ₂	4.93	5.00	45.55	45.35
CH ₃	5	86.0	57—60	C ₂₁ H ₄₀ N ₂ I ₂ · H ₂ O	4.85	4.73	43.27	42.95
CH ₃	6	93.5	247—249	C ₂₂ H ₄₂ N ₂ I ₂ · H ₂ O	4.41	4.62	41.80	41.91
CH ₃	7	87.0	231—233	C ₂₃ H ₄₄ N ₂ I ₂	4.48	4.65	42.28	42.19
CH ₃	9	63.5	250—252	C ₂₅ H ₄₈ N ₂ I ₂ · H ₂ O	4.32	4.52	39.15	39.20
CH ₃	10	92.2	249—251	C ₂₆ H ₅₀ N ₂ I ₂	4.44	4.35	39.60	39.44
C ₆ H ₅	4	97.0	55	C ₃₀ H ₄₂ N ₂ I ₂	4.04	4.08	37.05	37.13
C ₆ H ₅	5	94.5	113—115	C ₃₁ H ₄₄ N ₂ I ₂ · H ₂ O	3.61	3.9	35.52	35.42
C ₆ H ₅	6	92.3	261—263	C ₃₂ H ₄₆ N ₂ I ₂	3.89	3.93	35.70	35.67
C ₆ H ₅	7	69.0	82	C ₃₃ H ₄₈ N ₂ I ₂	3.57	3.76	33.89	34.14
C ₆ H ₅	9	73.2	67	C ₃₅ H ₅₂ N ₂ I ₂	4.14	4.24	—	—
C ₆ H ₅	10	75.0	188—190	C ₃₆ H ₅₄ N ₂ I ₂	3.54	3.64	—	—
C ₆ H ₅ CH ₂	4	93.4	251—253	C ₃₂ H ₄₆ N ₂ I ₂	3.76	3.93	35.67	35.66
C ₆ H ₅ CH ₂	6	97.5	210—212	C ₃₄ H ₅₀ N ₂ I ₂	3.83	3.78	34.50	34.32
C ₆ H ₅ CH ₂	7	97.7	179—181	C ₃₅ H ₅₂ N ₂ I ₂	3.53	3.72	33.78	33.68
C ₆ H ₅ CH ₂	9	79.5	220—222	C ₃₇ H ₅₆ N ₂ I ₂	3.41	3.58	32.54	32.48
C ₆ H ₅ CH ₂	10	88.8	235—237	C ₃₈ H ₅₈ N ₂ I ₂	3.44	3.51	32.14	31.91
OCOCH ₃	4	97.8	235—237	C ₂₂ H ₃₈ O ₄ N ₂ I ₂	4.45	4.33	39.25	39.20
OCOCH ₃	6	96.2	240—242	C ₂₄ H ₄₂ O ₄ N ₂ I ₂	4.40	4.14	37.77	37.57
OCOCH ₃	10	92.0	184—187	C ₂₈ H ₅₀ O ₄ N ₂ I ₂	3.80	3.82	34.77	34.69

TABLE 2



R	n	X	Yield %	M.p.	Empirical formula	% N		% X	
						Found	Calc.	Found	Calc.
H	1	I	81.7	287°	C ₁₆ H ₃₀ ON ₂ I ₂	5.50	5.39	48.40	48.84
H	2	I	71.0	272—274	C ₁₈ H ₃₄ ON ₂ I ₂	5.06	5.11	46.16	46.35
CH ₃	1	I	91.5	211—212	C ₁₈ H ₃₄ ON ₂ I ₂	5.05	5.11	—	—
CH ₃	2	I	81.2	208—210	C ₂₀ H ₃₈ ON ₂ I ₂	4.83	4.86	44.50	44.10
C ₆ H ₅	1	Br	78.5	182	C ₂₈ H ₃₈ ON ₂ Br ₂	4.65	4.85	27.61	27.68
C ₆ H ₅ CH ₂	1	Br	97.3	72	C ₃₀ H ₄₂ ON ₂ Br ₂	4.62	4.62	26.20	26.42
OCOCH ₃	2	I	88.7	93—95	C ₂₂ H ₃₈ O ₅ N ₂ I ₂	4.32	4.22	38.15	38.25

Heptamethylene-bis-quinuclidinium iodide. One g of quinuclidine, 1.58 g of diiodoheptane, and 4 ml of anhydrous alcohol were boiled for six hours. When the solution was cooled, a precipitate of the diquaternary salt came down which was filtered off, washed with alcohol, and dried. Yield 1.9 g (70%). Colorless crystalline powder, easily soluble in alcohol and water, insoluble in acetone, ether. M.p. 211–213° (from a mixture of acetone and alcohol).

By this method we obtained other diquaternary quinuclidinium salts (Table 1) and also analogous compounds which contained an oxygen function in the polymethylene chain (Table 2).

SUMMARY

We have described the synthesis of diquaternary salts: polymethylene bis-quinuclidinium halides and analogous compounds which contain oxygen functions in the polymethylene chain.

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STUDIES IN THE FIELD OF MONORGANOSILANES

II. THE REACTIVITY OF MONOORGANOSILANES IN REACTION WITH ALCOHOLS

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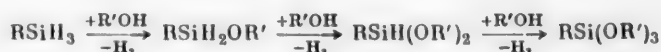
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 8,
pp. 2613-2618, August 1961

Original article submitted July 8, 1960

The properties of the monoorganosilanes RSiH_3 have still been very little studied, although, as we have already noted [1], a study of the properties of these compounds is of great theoretical and practical interest. It is known that the monoorganosilanes have a more labile Si-H bond than do the di- and triorganosilanes and react more easily under the influence of nucleophilic reagents. Thus, Stock and Somiesky [2] found an energetic reaction of methylsilane with alcoholic solutions of alkali, Nebergall [3] noted an easy reaction with halogens, and later, with alcohols [4]. We observed that these substances react very easily with different amines and their derivatives.

However, no one has undertaken a systematic study of these reactions to establish their mechanism and rules.

For an explanation of the reactivity of different monoorganosilanes and the relative reactivity of the Si-H bond depending on the number and nature of the radicals on the silicon atom, we undertook the study of the kinetics of the reaction of monoorganosilanes with alcohols. This reaction can be represented by the general scheme:



As the objects of study we chose butylsilane, phenylsilane, *p*-chlorophenylsilane, and for alcohols, propyl, allyl, propargyl, and benzyl. The reaction kinetics were studied by the rate of evolution of hydrogen formed in the reaction of monoorganosilanes with alcohols in the presence of a strictly determined amount of catalyst, freshly precipitated metallic copper, and at different temperatures: 10, 20, 30, and 40°.

TABLE 1. Reaction Rate Constants of Monoorganosilanes with Alcohols

Alcohol	20°			40°		
	$1/h = k_1$ per k_2	$k_1 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹	$k_2 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹	$1/h = k_1/k_2$	$k_1 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹	$k_2 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹
Phenylsilane						
Propyl	29.0	7.34	2.53	11.7	11.7	10.0
Benzyl	13.6	0.914	0.672	10.2	1.20	1.17
Allyl	9.6	2.60	2.70	8.5	3.29	3.87
Propargyl	1.73	0.0287	0.0345	8.3	0.0747	0.431
<i>p</i> -Chlorophenylsilane						
Propyl	7.5	2.23	2.97	12.7	4.58	3.60
Benzyl	16.9	0.636	0.376	13.7	0.922	0.672
Allyl	5.95	1.49	2.50	6.1	3.32	5.44
Propargyl	0.2	0.00559	0.277	0.2	0.0238	1.19

The experimental results from 66 experiments (Fig. 1) show that in the great majority of cases in the initial stages there is rapid evolution of hydrogen. Then it slows down and finally stops entirely. It was shown that at molar

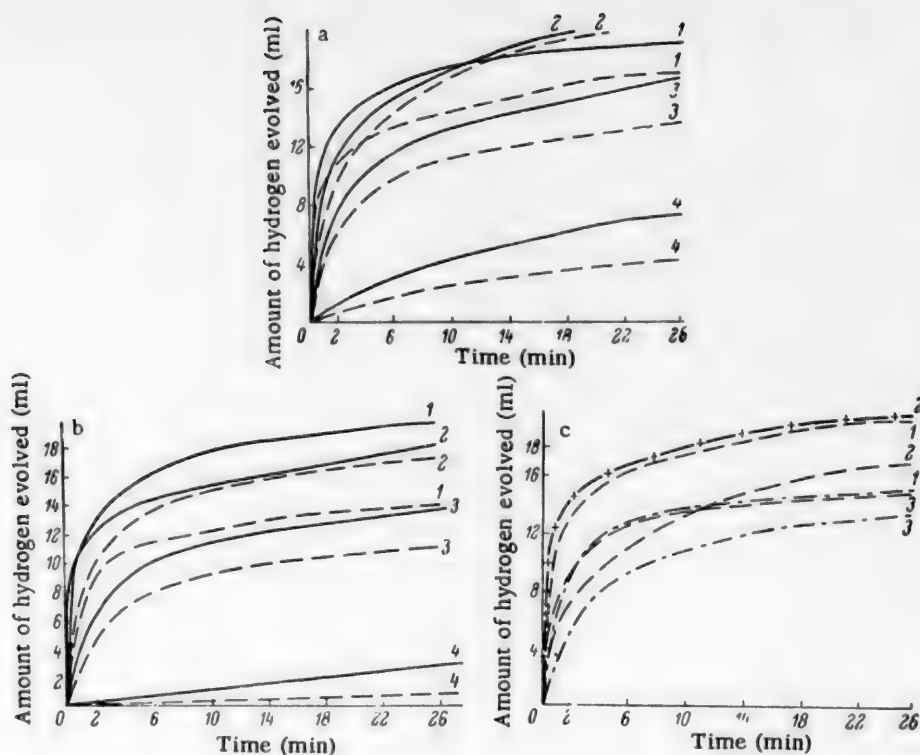


Fig. 1. Reaction kinetics of monoorganosilanes with alcohols. a) phenylsilane; b) *p*-chlorophenylsilane; c) butylsilane. Reaction temperatures: —, 10°; ---, 20°; -X-X-, 30°; ···, 40°. Alcohols: 1) propyl; 2) allyl; 3) benzyl; 4) propargyl.

TABLE 2. Reaction Rate Constants for Butylsilane with Alcohols

Alcohol	10°			20°			30°		
	1/k	$k_1 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹	$k_2 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹	1/k	$k_1 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹	$k_2 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹	1/k	$k_1 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹	$k_2 \cdot 10^3$ liter mole ⁻¹ sec ⁻¹
Propyl	7.1	1.75	2.46	14.3	5.05	3.53	—	—	—
Benzyl	8.3	0.539	0.649	17.8	1.82	1.02	—	—	—
Allyl	—	—	—	11.0	1.28	1.66	16.5	8.93	5.41
Propargyl	Does not react								

ratio of monoorganosilane: alcohol = 1:3; the maximum evolution of hydrogen is 2/3 the theoretically possible. Thus we can consider that under the conditions chosen for the experiments only the first and second hydrogens of the monoorganosilanes react, that is, there is not a three stage reaction, but only a two stage one.

This is in accord with the results of Nebergall [4] who in no case could isolate a phenyltrialkoxysilane in the reaction of phenylsilane with alcohols.

It was also shown that butylsilane does not react at all with propargyl alcohol.

For an estimation of the reactivity of the Si-H bond we took the value of the apparent energy of activation of the first (E_1) and second (E_2) reaction. The rate constants of the reactions

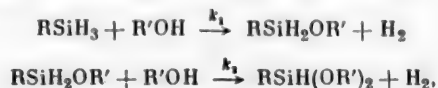


TABLE 3. Apparent Activation Energies of the Reaction of Organosilanes RSiH_3 with Alcohols, E_1 and E_2 (cal/mole)

Alcohol	Activation energy of first reaction, E_1			Activation energy of second reaction E_2		
	R			R		
	Phenyl	p-Chlorophenyl	Butyl	Phenyl	p-Chlorophenyl	Butyl
Propyl	4274	6539	17570	12584	4854	5976
Benzyl	2784	3584	20174	5686	5622	7488
Allyl	2156	7758	17690	3298	7522	14022
Propargyl	8705	13376	—	25087	13376	—

TABLE 4

Alcohol	E_1 (cal/mole)	E_2 (cal/mole)	ΔE (cal/mole)	E_1/E_2
Propyl	6539	4854	-1685	1.35
Allyl	7758	7522	-236	1.03
Propargyl	13376	13376	0	1.00
Benzyl	3584	5622	+2038	0.64

which occur in parallel and successively, were calculated by the method of Frost and Schwemer [5] using our table. The resulting values for the first and second rate constants of the reactions of the silanes studied with alcohols at different temperatures are given in Tables 1 and 2.

On the basis of these results we determined analytically for all the pairs of reagents studied the value of the apparent energy of activation of the first and second reactions. These values are given in Table 3.

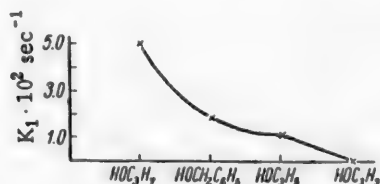


Fig. 2*. Dependence of rate constant of first reaction of butylsilane on structure of the alcohol.

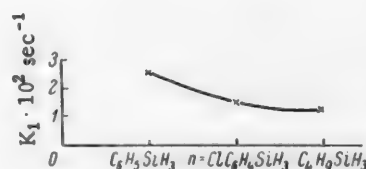
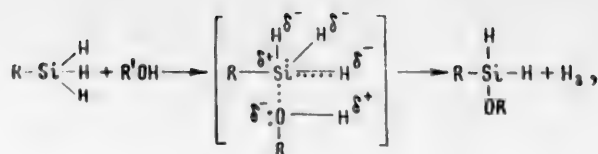


Fig. 3. Dependence of rate constant of first reaction of allyl alcohol on structure of the silane.

For the reaction of triorganosilanes with alcohols a mechanism of nucleophilic substitution is assumed (type $\text{S}_{\text{N}}2$ of Ingold-Hughes) [6]. In our case it is also possible to assume that the reaction occurs by such a mechanism. Analysis of the kinetic data favors this. Thus, we find a decrease in reaction rate with decreased degree of nucleophilic character of the attacking agent (Fig. 2) and a decreased reaction rate with lessened electrophilic character of the radical connected with the hydrogen which splits off (Fig. 3). Here the reaction mechanism can be represented by the scheme set up for a nucleophilic attack on the silicon atom by the alkoxyl, with formation of an activated complex and then occurrence of the Si-O bond with splitting of a hydrogen molecule.

*In Figs. 2,3,4 the dimensions of k_1 are liter mole $^{-1}$ sec $^{-1}$



From this scheme it follows that the less the electron density on the silicon atom and the greater the electron density on the oxygen atom of the alcohol, the easier should be the reaction and the lower should be the energy of activation.

TABLE 5

Alcohol	Propyl	Benzyl	Allyl	Propargyl
$k_1 \cdot 10^2$ (liter mole ⁻¹ sec ⁻¹)	2.23	0.636	1.49	0.0056
E_1 (cal/mole)	6539	3584	7758	13376

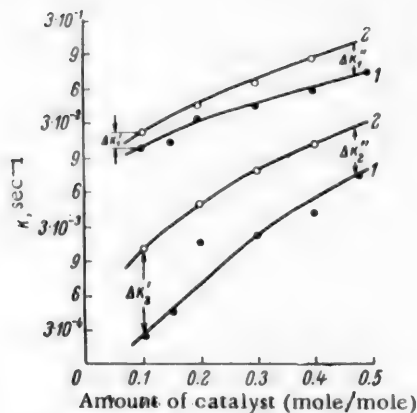


Fig. 4. Dependence of reaction rate constant of *p*-chlorophenylsilane with propyl alcohol on amount of catalyst. Temperature: 1) 20° 2) 40°

On the basis of the experimental data about the size of the activation energy and the assumption of this scheme for the reaction mechanism, the following conclusions can be drawn.

The energy of activation of the first reaction E_1 rises for all the alcohols depending on the nature of the organic radical in the silane in the order $C_6H_5 < p\text{-ClC}_6H_4 < C_4H_9$. Hence the reactivity of the organosilanes will fall in the order $C_6H_5SiH_3 > p\text{-ClC}_6H_4SiH_3 > C_4H_9SiH_3$.

The activation energy of the second reaction, E_2 , does not change regularly due to the different character of the influence of the already added alkoxy radicals.

Comparison of the values of E_1 and E_2 for the reaction of individual monoorganosilanes with different alcohols permits an estimation of the degree of influence of the added alkoxy radicals, and hence also the relative size of the negative charge on the atom of oxygen of the corresponding alcohol. For the reaction of *p*-chlorophenylsilane with different alcohols, see Table 4.

Hence, from these indexes, the alkoxy radicals can be arranged in the following order $C_3H_7O^- > C_3H_5O^- > C_3H_3O^- > C_6H_5CH_2O^-$. This series has general significance and characterizes the reactivity of the studied alcohols in reactions of nucleophilic substitution.

If we take as the criterion of reactivity the value of the rate constant, then in some cases there will not be agreement with the regularities established from the energy of activation. In the case of *p*-chlorophenylsilane, see Table 5.

Certainly here there is an effect of a special factor which makes difficult the attack on the silane by the alkoxy where there is the large group $CH_2-\text{C}_6H_4$.

It is necessary to remark that the kinetic values found by us are relative, since the reaction occurs in the presence of a heterogeneous catalyst. The amount of catalyst has an effect on the value of the first and second rate constants of the reaction and the energy of activation, as Fig. 4 shows, where we give the results for the reaction between *p*-chlorophenylsilane and propyl alcohol.

Here the effect of the catalyst on the second reaction is greater than on the first, the activation energy of the first reaction rises with increasing amount of catalyst, and that of the second reaction falls. Evidently the theoretical conclusions drawn above would be baseless if they were not founded on experiments carried out with strictly determined and constant (0.2 mole/mole) amounts of catalyst.

The description of the isolation and characterization of the reaction products in the reactions which we have studied will be the subject of further communications.

EXPERIMENTAL

Starting products. Butylsilane, phenylsilane, and *p*-chlorophenylsilane were synthesized by reduction of the corresponding monoorganotrichlorosilanes with lithium hydride, as we have previously described [1]. Propyl, allyl, propargyl, and benzyl alcohols were carefully dried and fractionated; we obtained products with constants which agreed exactly with the data in the literature. The catalyst, powdered copper, was prepared by reduction of copper sulfate with zinc dust [7], with later drying of the precipitate in a vacuum desiccator at room temperature.

Kinetic measurements; The experiments were carried out in a Chugaev-Tserevitinov apparatus. In one leg of the reaction apparatus we placed a sample of the silane and the catalyst, in the other, an equimolar amount of the alcohol. The reactor was joined through a reflux condenser to a Lunge nitrometer and placed in a water thermostat in which the desired temperature was maintained with an accuracy of $\pm 0.2^\circ$.

Reaction occurred with continuous mixing, and the amount of hydrogen evolved was recorded every 10-15 seconds.

In all we carried out 66 experiments, the data for which are given in Fig. 1.

SUMMARY

1. We have studied the reaction kinetics for three monoorganosilanes with alcohols of different structures in the presence of metallic copper. We have shown that the reaction occurs in a two step parallel-successive reaction of the second order.

2. We have determined the rate constants of the first and second reactions and the corresponding apparent energy of activation. We have suggested that the reaction of monoorganosilanes with alcohols occurs by a mechanism of nucleophilic substitution of type S_N2 and have established a number of effects of the substituent on the silicon atom on the reactivity of the Si-H bond.

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COMPOUNDS WITH POTENTIAL ANTITUBERCULOSIS ACTIVITY

II. N-SUBSTITUTED THIOAMIDES OF THIAZOLCARBOXYLIC ACIDS

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In order to widen the search for antituberculosis drugs among the thioamides of heterocyclic acids, we have carried out the synthesis of thiazole derivatives which contain thioamide groups substituted on nitrogen, especially the thioanilides of thiazolcarboxylic acids. Such substituted thioamides and also the corresponding amides have not been described in the thiazole series.

The thioanilides of 4- and 5-thiazolcarboxylic acids were obtained by the action of phosphorus pentasulfide in pyridine on the corresponding anilides. The latter were obtained in satisfactory yields by heating the acids with phosphorus oxychloride and aniline (or *p*-phenetidine). The reaction of N-substituted amides of thiazolcarboxylic acids with phosphorus pentasulfide took place with greater difficulty than did the analogous reaction in the series of other heterocyclic compounds or benzene [1,2]: for replacement of oxygen by sulfur, long heating (10-14 hours or more) of the reaction mixture at the boiling point was required, and the yield of pure products was usually small.

Substituted thioamides of 2-thiazolcarboxylic acid were obtained by us using the Wilgerodt-Kindler reaction, by interaction of 2-methylthiazole with sulfur and amines [3]. This reaction has not previously been carried out in the thiazole series. We obtained the starting 2-methylthiazole with a yield up to 57% by condensation of chloroacetaldehyde with thioacetamide [4], and in place of the monomer we used the dimer of chloroacetaldehyde [5].

In the syntheses we used aniline, *p*-anisidine, *p*-phenetidine, *p*-toluidine, 2-aminopyridine, α -naphthylamine, morpholine, and others. As a result of the reaction, in most cases we obtained the corresponding N-substituted thioamides of 2-thiazolcarboxylic acid, clear yellow, crystalline substances; however, the yields were lower than when carrying out the analogous reaction with 2- and 4-picolines [6] and did not exceed 25% on the amines used; in all the experiments a considerable amount of sulfur separated reversibly, almost equal to the amount originally taken; this shows the partial destruction of the thiazole ring.

The best yield of thioamides was obtained by heating the mixture of components in the ratio: 2 moles of 2-methylthiazole: 1 mole amine: 3 moles sulfur for 20-30 hours at 130-140°; at higher temperatures we observed the formation of insoluble, high melting polymers.

Treatment of the reaction mass was carried out by three methods. In the first process, the tarry mass which remained after distillation with steam of the unreacted starting substances, was treated with a hot solution of alkali, from which the thioamide was isolated by acidification (Table 2, compounds I and IV).

The substituted thioamides (V and VII) were obtained in the reaction of α -naphthylamine and morpholine with 2-methylthiazole and were insoluble in alkali; therefore, for their isolation the reaction mass was treated with alcohol (or ether), the sulfur was separated, and from the alcohol solution after repeated crystallizations we obtained the pure substances. Finally, thioamides (II, III, and VI) which contained the residues of *p*-anisidine, *p*-phenetidine, and α -aminopyridine, were separated by treatment with concentrated hydrochloric acid through the hydrochlorides which were easily hydrolyzed by washing with water.

Attempts to obtain the corresponding thioanilides by reaction of 2-methylthiazole with sulfur and *p*-nitroaniline (analogously to the similar reaction in the pyridine series [6]) did not give positive results. We also could not carry out the reaction of 2-methylthiazole with dimethylformamide [7] and isonicotinoylhydrazine [8]; in the first case we recovered the starting substance, in the second case we obtained diisonicotinoylhydrazone.

In a recently published short communication [3] we showed that we could not detect derivatives of benzthiazole which could be formed as by-products in the Wilgerodt-Kindler reaction. However, in later experiments on preparing

the thioanilide of 2-thiazolcarboxylic acid (I) after modifying the treatment of the reaction mass of the tarry residue from alkaline extraction we isolated a very small amount of a substance which was the expected 2-(thiazolyl-2')-benzthiazole. This confirms the fact that the reaction of 2-methylthiazole with sulfur and amines occurs by the same path as in the pyridine series.

All our N-substituted thioamides, and also the anilides of thiazolcarboxylic acids were subjected to a chemotherapeutic study. *

The anilides did not show marked antibacterial or fungicidal action. Most of the thioamides were very weakly active as bacteriostatic agents in vitro toward Mycobacterium tuberculosis.

Considerable antituberculosis activity (minimum bacteriostatic dilution in the absence of serum was 1:8 million) was shown by the p-methoxythioanilide of 2-thiazolcarboxylic acid, but the activity of this preparation fell very sharply with serum (dilution of 1:28,000).

The most active compound in the experiments in vitro was the thioanilide of 2-thiazolcarboxylic acid. This compound inhibited the growth of the tuberculosis bacteria in dilutions of 1:1 million in the presence of serum. However, in experiments on animals the preparation did not show healing action.

For comparison of chemotherapeutic activity we obtained and studied the unsubstituted thioamide of 2-thiazolcarboxylic acid [9]; we showed that this preparation was very weakly active. Thus, in the thiazole series we find an effect contrary to that which was observed for the thioamides of the pyridine series; the introduction of a phenyl radical on the nitrogen of the thioamide group did not lower, but strengthened the activity of the preparation in vitro. Other substituents had a very weak effect on the activity of the compounds. A shift in the thioanilide group from position 2 to position 4 or 5 of the thiazole ring also lowered the activity sharply.

EXPERIMENTAL

Anilide of 4-methyl-5-thiazolcarboxylic acid. To a mixture of 5 g of 4-methyl-5-thiazolcarboxylic acid and 3.28 g of aniline we added gradually with stirring 4.83 g of phosphorus oxychloride. Then the partly solidified reaction mass was heated to 110-120° with periodic stirring; at about 100° an intense reaction began, accompanied by foaming; after the reaction stopped, the dark, viscous mass was transferred to 100 ml of water and left for several hours to full crystallization. The crystals were filtered off, washed with 5% sodium bicarbonate solution, and recrystallized from 50% alcohol. We obtained 3.6 g of anilide with m.p. 156-158° (Table 1).

Analogously we obtained the anilides of 2-methyl-5-thiazolcarboxylic acid, 4-thiazolcarboxylic acid, 5-thiazolcarboxylic acid, and p-ethoxyanilide of 4-methyl-5-thiazolcarboxylic acid.

Thioanilide of 4-methyl-5-thiazolcarboxylic acid. To a boiling solution of 1 g of anilide of 4-methyl-5-thiazolcarboxylic acid in 5 ml of anhydrous pyridine with stirring, we added in portions 0.5 g of P₂S₅. The mixture was heated at 125-130° (bath temperature) for ten hours, then the reaction mass was poured into 50 ml of water and left for several days to full crystallization. After recrystallization from benzene we obtained 0.5 g of substance with m.p. 161.5-162° (Table 1).

Thioanilide of 2-thiazolcarboxylic acid and 2-(thiazolyl-2')-benzthiazole. A mixture of 20 g of 2-methylthiazole (b.p. 126-130°), 10 g of sulfur, and 10 g of aniline was heated with stirring for 29 hours (bath temperature 130-140°). Unreacted methylthiazole and aniline were removed with steam. From the water distillate after salting out with potash and extraction with ether we obtained 14 g of a mobile liquid with b.p. 126-140° which was methylthiazole with a small admixture of aniline.

The residue from the steam distillation was a thick, partly crystalline oil which was treated with ether. After removal of the ether, insoluble sulfur (7 g), the ether solution was dried, the solvent was removed, the residue was treated (3 times with 25 ml) with hot 3N KOH solution. From the alkaline extract after acidification with concentrated HCl we obtained 5.2 g of thioanilide of 2-thiazolcarboxylic acid in the form of yellow crystals with m.p. 65-73° (yield 22%, calculated on the aniline). Recrystallization from 50% alcohol gave a substance with m.p. 75.5-77°. Part of the reaction mass did not dissolve in alkali and was removed with ether; from the ether solution we obtained 0.1 g of a mixture of crystalline substance and tar. After pressing on a porous plate and recrystallizing from alcohol we obtained colorless crystals with m.p. 144-146°, which were 2-(thiazolyl-2')-benzthiazole.

Found %: C 55.18; H 3.10; N 12.89; S 29.22. C₁₀H₆N₂S₂. Calculated %: C 55.0; H 2.75; N 12.84; S 29.35.

* The biological study was carried out in the Division of Chemotherapy of the VNIKhFI by T. N. Zykova, and S. N. Milovanova under the direction of G. N. Pershin.



TABLE 1. Anilides and Thioanilides of 4- and 5-Thiazolcarboxylic acids

R	R ₁	R ₂	M.p. (from aqueous alcohol)	Empirical formula	% C		% H		% N		% S	
					Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
H	H	CONHC ₆ H ₅	136—137.5 [•]	C ₁₀ H ₈ ON ₂ S	58.82	59.16	3.95	4.02	13.72	13.60	15.70	15.85
H	H	CSNHC ₆ H ₅	160—161.5	C ₁₀ H ₈ N ₂ S ₂	54.51	54.48	3.66	3.42	12.71	12.67	29.11	28.98
H	CONHC ₆ H ₅	H	84—86	C ₁₀ H ₈ ON ₂ S	58.82	58.85	3.95	4.28	13.72	13.49	—	—
H	CSNHC ₆ H ₅	H	47.5—48.5	C ₁₀ H ₈ N ₂ S ₂	54.51	54.67	3.66	3.89	—	—	—	—
H	CH ₃	CONHC ₆ H ₅	156—158	C ₁₁ H ₁₀ ON ₂ S	60.53	61.13	4.57	4.60	12.72	12.84	14.55	14.37
H	CH ₃	CSNHC ₆ H ₅	161.5—162 [•]	C ₁₁ H ₁₀ N ₂ S ₂	56.37	56.55	4.30	4.44	11.95	11.83	—	—
H	CH ₃	CONHC ₆ H ₄ OC ₂ H ₅ -n	136—137	C ₁₃ H ₁₄ O ₂ N ₂ S	59.51	59.39	5.37	5.29	10.68	10.49	12.22	12.01
H	CH ₃	CSNHC ₆ H ₄ OC ₂ H ₅ -n	149—150 [•]	C ₁₃ H ₁₄ ON ₂ S ₂	56.08	56.27	5.06	5.03	10.06	10.03	—	—
CH ₃	H	CONHC ₆ H ₅	160—161.5	C ₁₁ H ₁₀ ON ₂ S	60.53	60.59	4.61	4.68	12.83	13.00	14.69	14.54
CH ₃	H	CSNHC ₆ H ₅	167.5—169 ^{••}	C ₁₁ H ₁₀ N ₂ S ₂	56.37	56.21	4.30	4.00	—	—	27.37	27.57

•From benzene

••From dichloroethane

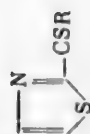


TABLE 2. N-Substituted Thioamides of 2-Thiazolcarboxylic Acid

Compound number	R	M.p. (from 50% alcohol)	Empirical formula	% C		% H		% N		% S	
				Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
(I)	NHC ₆ H ₅	75.5—77°	C ₁₀ H ₈ N ₂ S ₂	54.51	54.86	3.66	3.74	12.71	12.73	29.11	29.16
(II)	NHC ₆ H ₄ OCH ₃ - <i>n</i>	62.5—63.5	C ₁₁ H ₁₀ ON ₂ S ₂	52.78	52.63	4.02	4.18	11.19	11.10	25.63	25.45
(III)	NHC ₆ H ₄ OC ₂ H ₅ - <i>n</i>	63.5—64.5	C ₁₂ H ₁₂ ON ₂ S ₂	54.53	54.32	4.57	4.67	10.60	10.48	24.27	24.76
(IV)	NHC ₆ H ₄ CH ₃ - <i>n</i>	114—115.5	C ₁₁ H ₁₀ N ₂ S ₂	56.36	56.3	4.30	4.43	11.95	11.69	27.37	27.3
(V)		167—168 from dioxane	C ₁₄ H ₁₀ N ₂ S ₂	62.19	62.42	3.72	4.07	—	—	23.72	24.04
(VI)		88—89	C ₉ H ₇ N ₃ S ₂	48.79	48.44	3.19	3.13	19.00	18.90	—	—
(VII)		90—92	C ₈ H ₁₀ ON ₂ S ₂	44.84	45.22	4.70	4.84	—	—	29.93	30.16

By an analogous method we obtained the other N-substituted thioamides of 2-thiazolcarboxylic acid (Table 2).

SUMMARY

1. For chemotherapeutic studies we carried out the synthesis of a series of undescribed anilides and thioanilides of 4- and 5-thiazolcarboxylic acids.

2. The reaction of 2-methylthiazole with sulfur and amines gave a series of N-substituted thioamides of 2-thiazolcarboxylic acid which have not been described in the literature.

3. In the study of the reaction of 2-methylthiazole with sulfur and aniline we isolated as a by-product 2-(thiazolyl-2')-benzthiazole.

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ALKYLAMINOETHYL ESTERS OF BENZILIC AND DIPHENYLACETIC ACIDS

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Many tertiary and quaternary dialkylaminoethyl esters of benzilic and diphenylacetic acids possess cholinolytic (atropine-like) activity. Some of these compounds are valuable medicinal agents. It is also known that by sequential substitution of the alkyl radicals on the nitrogen by hydrogen atoms in similar esters, the physiological activity gradually falls. However, the esters of benzilic acid have not been subjected to systematic investigation in this respect. Among them, only the *n*-butylaminoethyl ester has been described as a chemical compound [1]. The methyl and ethylaminoethyl esters have been mentioned only in the pharmacological literature [2]. The question of the influence on cholinolytic activity of the branching of the alkyl radical on the nitrogen has not been discussed in the literature at all.

We undertook the synthesis of esters of the general formula:



where R = CH₃, C₂H₅, *n*-C₃H₇, *iso*-C₃H₇, *n*-C₄H₉, *sec*.-C₄H₉ and *tert*.-C₄H₉

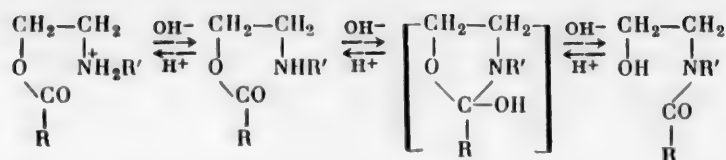
For comparison, one analogous ester of diphenylacetic acid was also synthesized.

In synthesizing these compounds, in contrast to the dialkylaminoethyl esters, one might expect difficulties due to the presence on the nitrogen of an aminoalcohol with a reactive hydrogen atom.

A number of methods are described in the literature for the synthesis of the esters of monoalkylaminoalcohols with various carboxylic acids. For example, it is recommended that they be prepared by heating a mixture of the hydrochloride of the aminoalcohol with the chloride of the acid without the use of a solvent [3,4] or in chloroform solution [5-8]. It is pointed out that it is possible to prepare these esters by the reaction of the chloride of an acid with the base of an aminoalcohol in the presence of a 5% solution of NaOH with subsequent rearrangement of the hydroxyethylamines which are formed to the hydrochlorides of the aminoethyl esters by boiling with concentrated HCl (Shotten-Baumann method) [9-13]. Blicke and Maxwell [1] refer to the synthesis of *n*-butylaminoethyl and unsubstituted aminoethyl esters of benzilic acid according to the method of Gorenstein and Pelike, i.e., by the reaction of the corresponding chloroethylamine with benzilic acid. However, as will be shown below, the data of these authors, in any case in relation to the first compound, appear to be in error. The preparation of a series of alkylaminoethyl esters of phenyl-(thienyl-2)-acetic and phenyl-(thienyl-2)-glycolic acids by the esterification of the methyl esters of these acids with alkylaminoethanol in the presence of sodium methylate has been described [14]. In this case the *N*-alkyl-*N*-hydroxyethylamides that are obtained rearrange to form the hydrochlorides of the alkylaminoethyl esters on treatment with hydrogen chloride in isopropyl alcohol. Finally, the preparation of the esters of the alkylaminoalcohols by the direct reaction of these alcohols with the corresponding acids in the presence of concentrated H₂SO₄ has been described [11].

Information on the stability of the aminoethyl esters is of considerable interest. Many authors have mentioned the ease of the transition of the free bases of β -aminoalcohols containing a secondary and especially a primary amino group, to the corresponding ethanolamides, and also the tendency of the latter to be converted into salts of the original aminoesters on treatment with strong acids [6-8,11,15-18].

The hypothesis has also been stated that these rearrangements proceed through an intermediate stage of an oxazolidine derivative, although the possibility of a direct transition of the acyl from the hydrogen to the nitrogen and vice versa is not excluded [17].



In order to synthesize the esters we made use of a considerable number of the methods mentioned above since no one of them individually seemed suitable in all cases. For example in preparing the methylaminoethyl ester of diphenylacetic acid the most suitable method appeared to be the reaction of the chloride of the acid with the hydrochloride of the aminoalcohol in chloroform solution which had previously been saturated with hydrogen chloride. The reaction product was the hydrochloride of the aminoester and was stable in aqueous solution. However, on alkalinizing the latter it was not the free base of the amino ester which separated out, but N-methyl-N-hydroxyethylidiphenylacetamide which is insoluble in acids. Experiment showed that the Schotten-Baumann reaction in this case was less convenient.

This method was found to be unsuitable for the synthesis of the alkylaminoethyl esters of benzoic acid. These esters were prepared, with varying degrees of success, by the following three methods.

Method A. The reaction of the chloride of diphenylchloroacetic acid with alkylaminoethanol in the presence of aqueous alkali (Schotten-Baumann), with subsequent hydrolytic cleavage of the chlorine and rearrangement of the hydroxyethylamide by the action of hydrochloric acid to the hydrochloride of the aminoester.

Method B: the reesterification of the methyl or ethyl ester of benzoic acid by means of alkylaminoethanol. In this case also the corresponding hydroxyethylamide is first formed which, by treatment with hydrogen chloride in ether solution, is converted into the hydrochloride of the aminoester.

Method C: the reaction of benzoic acid with chloroethylalkylamine by heating in a solution of chlorobenzene. In this case the hydrochloride of the aminoester is formed immediately.

Typical examples of syntheses by these methods are given in the experimental section.

In addition to the analytical data, the structure of the esters synthesized was confirmed in three cases by the results of their hydrolytic cleavage, as a result of which the corresponding acids and aminoalcohols were obtained in almost quantitative yield and were identified by their picrates.

The alkylaminoethyl esters of benzoic acid which were synthesized (see Table) were more resistant to rearrangement to form the hydroxyethylamides than the methylaminoethyl ester of diphenylacetic acid. Their free bases may be separated from aqueous solutions of the hydrochlorides by means of alkali in the form of comparatively high-melting crystals which may be kept a long time without noticeable change. However when heated above the melting point the majority of them are readily converted to substances which are insoluble in dilute acids and are apparently the corresponding hydroxyethylamides.

The hydrochloride of the n-butylaminoethyl ester of benzoic acid (VI) which we prepared, and which was described previously by Blicke and Maxwell [1], melted at 164-165.5°, and not at 121-122° as they indicated. Inasmuch as the structure of the compound we prepared was confirmed not only by analysis, but also by the results of its hydrolytic cleavage, one may justly doubt the data presented by Blicke and Maxwell.

The data given in the table are not favorable to synthesis method A (Schotten-Baumann). Method B (Gorenshtein and Pelike) appears more hopeful, although in the case of compound (II) it gave considerably poorer results than the other two methods.

EXPERIMENTAL

The acids, aminoalcohols and chloroethylalkylamines necessary for the synthesis were prepared by the methods described in the literature.

The hydrochlorides of β-chloroethyl-n-butylamine and β-chloroethyl-tert.-butylamine, which are not described in the literature, were prepared by heating the hydrochloride of the aminoalcohol with thionyl chloride in chloroform.

Alkylaminoethyl Esters of Diphenylacetic and Benzilic Acids

Compound No.	Formula	Yield in % by method			M.p. (solvent for crystallization)		Chlorohydrate		Calc. % Cl
		A	B	C	chlorohydrate	base	found % Cl	empirical formula	
I	$(C_6H_5)_2CHCOOCH_2CH_2NHC_3H_7$	47 ^a	—	—	149—150.5° (acetone)	—	11.63, 11.70	$C_{17}H_{19}O_2N \cdot HCl$	11.59
II	$(C_6H_5)_2C(OH)COOCH_2CH_2NHC_3H_7$	57	78	21	186.6—187.5° (ethanol)	99—100° (ethanol and ether)	11.12, 11.15	$C_{17}H_{19}O_3N \cdot HCl$	11.02
III	$(C_6H_5)_2C(OH)COOCH_2CH_2NHC_2H_5$	—	14	37	177.5—178° (ethanol and ether)	114—115° (ether)	10.64, 10.70	$C_{18}H_{21}O_3N \cdot HCl$	10.56
IV	$(C_6H_5)_2C(OH)COOCH_2CH_2NH(n-C_3H_7)$	r	r	40	146—147° (ethanol and ether)	78—80° (ether)	10.26, 10.33	$C_{19}H_{23}O_3N \cdot HCl^f$	10.13
V	$(C_6H_5)_2C(OH)COOCH_2CH_2NH[CH(CH_3)_2]$	14	50	60	184.5—185.5° (ethanol)	89—90° (acetone)	10.27, 10.32	$C_{19}H_{23}O_3N \cdot HCl$	10.13
VI	$(C_6H_5)_2C(OH)COOCH_2CH_2NH(n-C_4H_9)$	35	51	47	164—165.5° (chloroform and acetone)	68—70° (ether)	9.49, 9.56	$C_{20}H_{25}O_3N \cdot HCl^h$	9.74
VII	$(C_6H_5)_2C(OH)COOCH_2CH_2NH[CH(CH_3)C_2H_5]$	—	52	—	179.5—181° (ethanol)	73—74° (ether)	9.52, 9.79	$C_{20}H_{25}O_3N \cdot HCl$	9.74
VIII	$(C_6H_5)_2C(OH)COOCH_2CH_2NH[C(CH_3)_3]$	22	91	84	217—218° (ethanol)	97—98° (ether)	9.85, 9.92	$C_{20}H_{25}O_3N \cdot HCl$	9.74

Notes: a) This compound was obtained with the same yield from the chloride of the acid and from the hydrochloride of the aminoalcohol in chloroform solution. b) Found %: C 71.71, 71.67; H 6.71, 6.87. $C_{17}H_{19}O_2N$. Calculated %: C 71.57; H 6.71. c) Found %: N 4.42, 4.62. Calculated %: N 4.35. d) The aminoester was not formed by this method. e) Found %: C 72.97, 73.08; H 7.68, 7.70. $C_{19}H_{23}O_3N$. Calculated %: C 72.81; H 7.40. f) Found %: N 3.99, 4.02. Calculated %: N 4.00. g) Found %: C 73.54; H 7.82, 7.88. $C_{20}H_{25}O_3N$. Calculated %: C 73.38; H 7.70. h) Found %: N 3.69, 4.06. Calculated %: N 3.85.

The hydrochloride of β -chloroethyl-n-butylamine, b.p. 239-240° (from alcohol and acetone). Base b.p. 70° (23 mm) in contrast to the literature [1]: b.p. 113-116° (23 mm) which is apparently in error.

The hydrochloride of β -chloroethyl-tert-butylamine, m.p. 201-202° (from alcohol and acetone).

The methylaminoethyl ester of diphenylacetic acid (I). A solution of 3.75 g of methylaminoethanol in 15 ml of chloroform was cooled and saturated with hydrogen chloride. After the addition of a solution of 13.3 g of the chloride of diphenylacetic acid in 15 ml of chloroform, the mixture was heated in a sealed tube at 55° for 50 hours. The chloroform was distilled off and the remaining material washed with ether and recrystallized twice from acetone. The yield was 7.2 g. b) A solution of 4.6 g of the chloride of diphenylacetic acid in 20 ml of ether was added, with stirring and at 10°, to a solution of 1.5 g of methylaminoethanol and 2 g of NaOH in 20 ml of water. After standing for 30 minutes the precipitate of N-methyl-N-hydroxyethyl diphenylacetamide was filtered off and washed with water until it no longer gave an alkaline reaction. Yield: 4.2 g. M.p. 147° (from benzene).

Found %: N 5.41, 5.49. $C_{17}H_{19}O_2N$. Calculated %: N 5.20.

1.0 g of the amide was dissolved in 30 ml of benzene and 2.0 ml of a 30% alcohol solution of HCl was added. The mixture was boiled for four hours. The precipitate of the hydrochloride of the ester (I) was filtered off and washed with ether. Yield: 0.7 g.

The n-butylaminoethyl ester of benzoic acid (VI). (Method A). A solution of 5.3 g of the chloride of diphenylacetic acid in 20 ml of ether was added gradually, with vigorous stirring, to a solution of 2.35 g of n-butylaminoethanol and 2.0 g of NaOH in 20 ml of water at 0°. The mixture was stirred for 30 minutes and then 55 ml of 1 N H_2SO_4 was added and it was heated for four hours at 30°. The ether layer was separated from the aqueous layer, washed with water and dried for one hour over sodium sulfate. Then 4 ml of a 25% alcohol solution of HCl was added to it and the mixture allowed to crystallize until the following day. The crystals were filtered off and recrystallized from a mixture of chloroform and acetone. Yield: 2.57 g.

Other alkylaminoethyl esters were synthesized in an analogous manner except in the case of methylaminoethyl ester (II) where the length of the treatment with dilute H_2SO_4 was one hour.

The methylaminoethyl ester of benzoic acid (II). (Method B). 2.25 g of methylaminoethanol, 20 ml of anhydrous benzene and 1.25 ml of a solution of sodium methylate in methyl alcohol (containing 0.03 g of Na) were placed in a Claisen flask equipped with a dropping funnel. At a bath temperature of 80-82° and under a weak vacuum (150-170 mm) the methyl alcohol and benzene were distilled off. Then two portions of 5 ml of benzene each were added, which were also distilled off. The mixture was cooled and to it were added 4.84 g of the methyl ester of benzoic acid and 5 ml of benzene, after which it was again heated to 80-82°. Under a weak vacuum the benzene was gradually distilled off, while continually adding it through the dropping funnel, for two hours. During this period 40 ml of benzene were added. On completion of the addition and distillation of benzene, the material remaining in the flask was dissolved in ether, the solution washed three times with water, dried over potash for 30 minutes and then 4 ml of alcoholic HCl was added to it. The next day the precipitate of the hydrochloride of the aminoester was filtered off, washed with chloroform and then with ether, and dried. The yield was 5.0 g. This method of washing the hydrochloride with chloroform is not recommended for the synthesis of other esters.

The alkylaminoethyl ester was not obtained in an attempt to re-esterify the methyl ester of benzoic acid by n-propylaminoethanol. Instead of it a hydrochloride of unknown composition was obtained, with a m.p. of 151-152° and a chlorine content averaging 9.12% instead of 10.13% calculated for the hydrochloride of the propylaminoethyl ester of benzoic acid.

The isopropylaminoethyl ester of benzoic acid (V). (Method C). 8.45 g of the hydrochloride of β -chloroethylisopropylamine was shaken in a separating funnel with 12 ml of a 20% solution of NaOH in 25 ml of chlorobenzene. The chlorobenzene layer was separated and the aqueous layer again extracted with 15 ml of chlorobenzene. The combined chlorobenzene solutions were dried for a short time over anhydrous potash and filtered. The potash on the filter was washed with 6 ml of chlorobenzene which was combined with the remaining filtrate. To the chlorobenzene solution of the base β -chloroethylisopropylamine was added 11.2 g of benzoic acid. The mixture was heated at 100° for six hours. On cooling it was shaken with 32 ml of a 25% potash solution and then ether was added until the layers clearly separated. The aqueous layer was discarded and the chlorobenzene layer washed twice with a 25% potash solution (6 ml each time) and dried over anhydrous potash. The ether was distilled off, and then the chlorobenzene - in vacuo

(5-10 mm). The aminoester base was dissolved in a small quantity of alcohol, acidified with alcoholic HCl and diluted with ether. The hydrochloride of the aminoester was filtered off, washed with ether and dried. Yield: 10.3 g.

Hydrolytic cleavage of alkylaminoethyl esters of benzilic and diphenylacetic acids. Compounds (I, II, VI) were subjected to hydrolytic cleavage. 1.0 g of the hydrochloride of the aminoester was boiled with 20 ml of dilute HCl (1 : 1) for 2-4 hours. The next day the precipitate of acid was filtered off, washed with water and dried. The yield was close to quantitative. Benzilic and diphenylacetic acids were identified by mixed melting point tests with known samples. The acid aqueous filtrate from the acids was evaporated to dryness. The remaining material was mixed with an excess of finely pulverized NaOH and the aminoalcohol extracted with ether. After drying with potash, an alcoholic solution of picric acid was added to the extract until the reaction was acid. The pictrate of alkylaminoethanol was filtered off and recrystallized from alcohol. The yield of picrates was from 0.15-0.20 g. The picrates were also identified by mixed melting point tests with known samples.

SUMMARY

1. The possibility of using a number of methods for the synthesis of alkylaminoethyl esters of benzilic and diphenylacetic acids was studied.
2. Seven alkylaminoethyl esters of benzilic acid with alkyl radicals of various lengths and structures were synthesized and identified as the hydrochlorides and free bases, as was also the methylaminoethyl ester of diphenylacetic acid which had not been previously described in the literature.
3. In connection with the ester synthesis, the hydrochlorides of β -chloroethyl-n-butylamine and β -chloroethyl-tert.-butylamine, which had not previously been described, were prepared and the boiling point of the free base of the former was refined.

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A STUDY OF THE MECHANISM OF THE AUTO-OXIDATION OF POLYALKYLBENZENES

LIQUID PHASE AUTO-OXIDATION OF ISOPROPYL-O-XYLENES

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One of us [1] established the fact, by using the auto-oxidation of 1,4-diisopropylbenzene and 1,3,5-triisopropylbenzene as examples, that the relationship of the rate constants of the substitution α -hydrogen atoms by the OOH group is determined by the number of unoxidized alkyl radicals in the original hydrocarbon and the reaction products.

Our further studies, and also an analysis of the experimental data of a number of authors, with the aid of equations for irreversible-successive processes, showed that the oxidation of other *m*- and *p*-dialkylbenzenes to hydroperoxides, alcohols and even ketones proceeds in an analogous manner [2-4]. These mechanisms may be very simply explained on the basis of concepts developed by Bagdasar'yan [5], who was interested in the comparatively weak susceptibility of ROO· radicals to the influence of polar substituents, which had been discovered by Russell [6].

In continuing our studies [1,7] it seemed of interest to investigate the peculiarities of the auto-oxidation of polyalkylbenzenes containing alkyl groups located side by side.

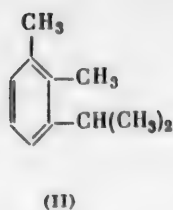
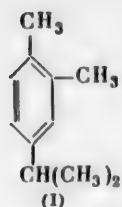
Taken per mole of hydrocarbon		Temperature	Oxidation time (in hours) and of hydrogenperoxide	Composition of the reaction mixture after reduction of the peroxides of sodium sulfite (mole %)								
Manganese resinate (in mg)	soda (in g)			hydrocarbon	dimethylxy- lylcarbinol	dimethyla- cetophenone	isopropyl- toluyllic acid	isopropyltol- ylcarbinols	lactones	hydroxyacid	keto acids	other pro- ducts with two oxi- dized gro- ups
10 *	1.5	120°	6 (16.5)	66.4	14.1	6.3	5.5	6.0	1.0	0.4	0.1	0.2
6 *	3.0	110	9 (23.0)	51.2	22.8	6.9	11.5	2.5	2.2	1.6	0.3	1.0
4 *	3.5	110	2 (15.1)	82.8	11.3	0.2	1.9	3.2	0.6	—	—	—
5 *	4.0	100	10 (16.3)	79.8	13.8	—	2.3	3.6	0.5	—	—	—
170 *	— ***	110	4 (1.2)	21.5	24.6	21.0	17.1	6.2	4.1	2.2	1.9	1.4
170 *	— ***	120	6 (0.7)	12.3	26.2	30.4	24.5	6.7	4.8	2.6	3.1	1.7
150 **	— ***	110	8 (0.5)	48.0	3.5	2.6	21.5	1.6	20.4	2.4		
10 **	3.0	110	15 (3.0)	74.0	2.9	2.5	12.3	0.9	9.4	—	—	—

*4-isopropyl-o-xylene was auto-oxidized.

**3-isopropyl-o-xylene was auto-oxidized.

***Cobalt acetate was used as an initiator.

The present paper is based on a study of the oxidation of 4-isopropyl-o-xylene (I) and 3-isopropyl-o-xylene (II) by the oxygen of the air in the presence of manganese resinate and cobalt acetate. As would be expected, compound (II), because of steric hindrance, oxidizes considerably more slowly than compound (I) (Fig. 1 and Table). On oxidizing compound (I), a tertiary and two primary hydroperoxides are formed. The latter, even when only partly oxidized, decompose and are converted into primary alcohols and acids. The radicals which appear during this

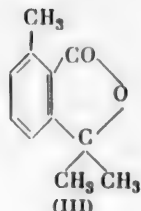


(and perhaps even molecules) induce the decomposition of the tertiary hydroperoxide. Indeed, if on the oxidation of triisopropylbenzenes, ketones and alcohols were obtained in significant quantities only on thorough oxidation [7], compound (I) would give 5-7 mole % of ketone at 30% oxidation. By means of a quantitative analysis of the oxidation products of compound (I) it was determined that in the early stages of the reaction the isopropyl group reacts with the peroxide radicals from 1.8-2.1 times faster than the two methyl groups. When the degree of oxidation increases, a tendency toward

equalization of the relative rates of oxidation of the tertiary and primary groups is observed. It is probable that this is connected with the fact that the radicals which are formed as a result of the decomposition of the peroxide compounds show less selectivity in attacking primary and tertiary α -carbon atoms than $\text{RCOO}\cdot$ radicals do. The rates of oxidation of methyl groups do not differ much from one another; however the CH_3 group, when located in a para position to an isopropyl, appears to be approximately 1.2 times more reactive than would be caused by polar factors and the effect of conjugation.

Isopropylxylene (I) gives comparatively few products with two oxidized groups (Acetyl- and α -hydroxyisopropyl-toluylic acid, isopropylphthalides, diols); the concentration of the majority of them becomes noticeable only when the degree of oxidation is greater than 30%, which would indicate that they are formed in succession. Isopropylxylene (II), on the other hand, even when the degree of oxidation is only slight, is converted into 3,3,7-trimethylphthalid with a yield of about 40% based on the hydrocarbon oxidized.

The formation of lactones in the process of liquid phase auto-oxidation of polyalkylbenzenes was observed by us for the first time [8].



EXPERIMENTAL

Isopropylxylenes were prepared by the alkylation of chemically pure o-xylene by propylene in the presence of $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$; this gave a mixture of isomers (I) and (II). Since 3-isopropyl-o-xylene (II) in the presence of $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$ at high temperatures, rapidly isomerizes into 4-isopropyl-o-xylene (I), the reaction temperature was maintained within the limits of 20-30° in order to get a satisfactory yield. The molar ratios of xylene, propylene and $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$ were 1.5-2 : 1 : 0.15-0.2; the yield of isopropylxylenes was 60-65%; the monoalkylate content of compound (II) was ~40%. The isomers were separated by repeated distillation through a column with an effectiveness of 45-50 theoretical plates.

In order to prepare 4-isopropyl-o-xylene (I), the alkylation was conducted with molar ratios of 2 : 1 : 0.2 at 60-80° and the yield of monoalkylate was 86-91%. Complete conversion of compound (II) to isomer (I) was achieved by stirring the mixture of isomers and $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$ for 5-6 hours at 80°.

Chemically pure hydrocarbons were used. This was determined by the aid of infrared absorption spectra in the 2000-1650 cm^{-1} range [8] and was also confirmed by oxidizing the hydrocarbons to polycarboxylic acids by means of nitric acid [10].

4-Isopropyl-o-xylene (I), had a b.p. of 199.5°, n_D^{20} 1.4995, d_4^{20} 0.8713, which correspond with the data in the literature [11].

The 3-isopropyl-o-xylene (II) had a b.p. of 204.5°, n_D^{20} 1.5102, d_4^{20} 0.8920.

Found %: C 89.26; H 10.69 M 149.0. $\text{C}_{11}\text{H}_{16}$. Calculated %: C 89.13; H 10.87, M 148.2.

The auto-oxidation was carried out by the method described [7] except for the fact that a graduated trap was used for determining the quantity of water that separated.

From 0.5-0.7 moles of hydrocarbon were ordinarily used for the auto-oxidation. Although by oxidizing (I) it is possible to obtain a reaction mixture containing 29% of hydroperoxide, one ought to reckon a concentration of 15-20% for the optimum degree of oxidation, since carrying it further increases the yield of by-products.

After oxidizing compound (I) to a given degree, peroxide compounds were quantitatively reduced by an excess of sulfite [1] and hydrocarbon (I) and its oxidation products were repeatedly extracted with ether and benzene. The aqueous phase was acidified with hydrochloric acid and the organic substances that separated (essentially acids) were

combined with the main mixture or analyzed separately. Then the mixture was treated with a solution of sodium bicarbonate, the soda extract was evaporated and acidified, and the organic acids extracted with ether. After washing with water, the extract was dried over sodium sulfate and the solvent distilled off. The material remaining contained a mixture that consisted principally of 2-methyl-4-isopropylbenzoic (IV) and 2-methyl-5-isopropylbenzoic (V) acids. At a greater degree of oxidation small quantities of α -hydroxyisopropyl- and acetyl-o-toluidic acids were detected in the acid fraction. The quantity of keto acids was determined by the formation of oximes; hydroxy acids were dehydrated to unsaturated acids by a modification of the method of Sokolov and others [12] in the presence of equal quantities of KHSO_4 and H_2SO_4 in a solution of diisopropylbenzene at 160-170°, while the water that separated was titrated by Fischer's reagent [13]. When a mixture of KHSO_4 and H_2SO_4 is used, the dehydration proceeds quantitatively and without tar formation. This method was also utilized for the determination of the relative quantities of mono- and di-, di- and trihydroxyderivatives of polyisopropylbenzenes which are not quantitatively dehydrated with KHSO_4 .

On standing, acid (IV) partially crystallizes from the mixture of acids; after recrystallization from petroleum ether it melts at 89°.

Found %: C 73.81; H 7.85 M 177.5. $\text{C}_{11}\text{H}_{14}\text{O}_2$. Calculated %: C 74.13; H 7.92. M 178.2.

Trimellitic acid with a m.p. of 228-232° (decomp.) was obtained by the oxidation of compound (IV) by means of 25% nitric acid in an autoclave. In order to determine the structure of compound (IV) it was also decarboxylated to m-cymene which, by oxidation with 15% nitric acid at atmospheric pressure gives m-toluidic acid with a m.p. of 110-111°, while oxidation in an autoclave gives isophthalic acid.

In order to identify acid (V) and to determine the molecular ratios of acids (IV) and (V), the mixture of acids was almost quantitatively decarboxylated in quinoline in the presence of copper (with soda-lime the yield of cymenes is 77-80%). The cymenes thus prepared were oxidized to phthalic acids which were separated by means of the barium salts or by their differential solubility in hot water (isophthalic acid was washed with water at 80°). The acids were identified as the dimethyl esters. The dimethylisophthalate melted at 67°; the dimethylterephthalate at 141°. Mixed melting point tests with known samples showed no depression.

The quantity of acid (IV) and acid (V) in the oxidation product amounted to 55 and 45% respectively. An effort to separate aldehydes from the reaction mixture by the use of bisulfite was not successful.

The mixture of organic materials remaining after separation of the acids was washed with cold 10% caustic soda in order to remove the phenols which were present in the mixture in very small quantities, and then it was treated with a solution of alkali and heated. This caused the hydrolysis of 5- and 6-isopropylphthalids which are practically insoluble in soda and cold alkali. The salts of hydroxyacids were acidified by hydrochloric acid and boiled for two hours under a reflux condenser; the lactones that were formed were extracted with ether, washed free of small quantities of acids, dried, and distilled in vacuo. B. p. 145-150° at 3 mm, M 174.0, n_D^{20} 1.5290, d_4^{20} 1.09.

The yield of lactones relative to the oxidized hydrocarbon was 3-5%. We did not succeed in separating the isomeric lactones nor in determining their relative quantities. In the majority of experiments we were limited to the analytical determination of the total quantity of lactones according to the following method which we worked out, a weighed sample of the substance was hydrolyzed by heating with 1 N caustic soda and the excess of alkali titrated. Then a definite quantity of hydrochloric acid was added to the mixture which was heated under a reflux condenser for 1.5-2 hours. During this period the hydroxyacids were quantitatively converted into neutral lactones. The mixture was diluted with alcohol, in which all organic acids may be titrated, and the excess acid determined by titration. From the decrease in its concentration, the phthalid content could be calculated. This method, which was tested on artificial mixtures, makes it possible to determine phthalid and its derivatives in the presence of acids, esters and other compounds.

The mixture, after being freed of lactones, consisting of hydrocarbon (I), 3,4-dimethylacetophenone (VI), dimethyl-4-o-xylyl-carbinol (VII), 2-methyl-4-isopropylbenzyl (VIII) and 2-methyl-5-isopropylbenzyl (IX) alcohols and also a small quantity of diols and ketoalcohols, was separated into three fractions by distillation: a) a hydrocarbon fraction, b. p. 88-90° at 18 mm; b) a mixture of compounds (VI-IX) with a b.p. of 100-125° at 5 mm, and c) a mixture of diols and ketoalcohols boiling at 125-140° at 3 mm.

The quantity of compound (VI) in the second fraction was determined by formation of the oxime; ketone (VI) was identified by means of the 2,4-dinitrophenylhydrazone, m. p. 253° (from toluene), which corresponds with the data in the literature [14].

The quantity of compound (VII) was determined by the quantity of water that was formed on dehydration. Special experiments indicated that primary alcohols do not interfere with this determination. It was not possible to obtain compound (VII) in a completely pure state. Its structure was established by converting it to 3,4-dimethylisopropenylbenzene (with the aid of KHSO_4) which, on oxidation, was converted into compound (VI) and 3,4-dimethylbenzoic acid, m. p. 166° . During vacuum distillation compound (VII) was partially converted into compound (X), and therefore the quantity of product (X) in the second fraction was determined by bromination in chloroform and methanol. On drawing up the balance, the quantity of compound (X) was counted over to compound (VII).

The primary alcohols (VIII) and (IX) were determined by acetylation with a 12% solution of acetic anhydride in pyridine, or by the reaction with phthalic anhydride [15]. The separation of alcohols (VIII) and (IX) from fraction (b) was accomplished by means of the phthalic ester. It was not possible to separate alcohols (VIII) and (IX); the esters of the alcohols obtained by hydrolysis were converted into the corresponding acids (IV) and (V) or directly to cymenes by heating with caustic potash up to 200° . According to the literature, this conversion takes place without isomerization [16]. The ratio of alcohols (VIII) and (IX) was approximately the same as that of acids (IV) and (V).

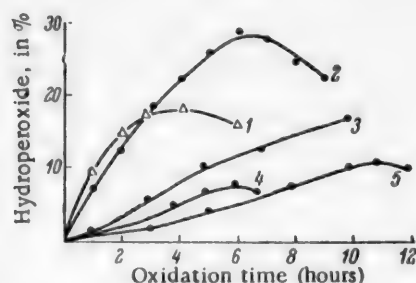


Fig. 1. Dependence of the kinetics of auto-oxidation of 4-isopropyl-o-xylene (curves 1-3) and 3-isopropyl-o-xylene (curves 4 and 5) on experimental conditions. 1) 10 mg-moles of manganese resinate, 1.5 g-moles of soda 120° ; 2) 6 mg-moles of manganese resinate, 3 g-moles of soda, 110° ; 3) 5 mg-moles of manganese resinate, 3 g-moles of soda, 110° ; 4) 10 mg-moles of manganese resinate, 2 g-moles of soda, 115° ; 5) 5 mg-moles of manganese resinate, 3 g-moles of soda, 110° .

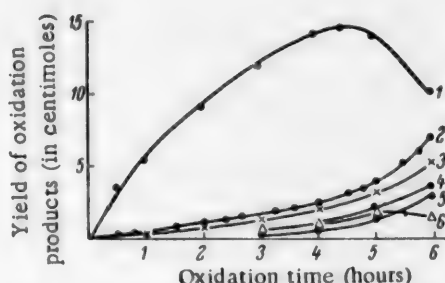


Fig. 2. Kinetics of the formation of auto-oxidation products of 4-isopropyl-o-xylene at 110° in the presence of 5 mg-moles of manganese resinate and with an air flow-rate of 1 liter/min. 1) hydroperoxides, 2) water; 3) acids; 4) tertiary alcohols; 5) ketones; 6) primary alcohols.

Analysis of the diol and ketoalcohol fractions was not carried out in detail; only their molecular weight and the number of functional groups were determined.

Besides the method of studying the oxidation products which has been described, we carried out a direct analytical determination of the reaction products in selected samples, and also an analysis of the reaction mixture after reduction of the peroxides and partial separation of the reaction products (after separating out the acids, distilling off the hydrocarbon, etc.). The hydroperoxides were determined iodometrically; the acids by titration with 0.1 N caustic soda in alcohol in the presence of phenolphthalein; alcohols, lactones and ketones - by the methods described above.

The results of the most characteristic experiments on the oxidation of compound (I) are shown in the Table and in Figures 1-3.

We also studied the cleavage of the hydroperoxide of compound (I) by acids. 100 g of the hydroperoxide of compound (I) was decomposed at a temperature below 50° in the presence of 0.1 g of sulfuric acid. The acid was neutralized with 0.4 g of soda, the mixture dried over sodium sulfate and then the acetone driven off, which amounted to 4.3 g (68%). (2,4-Dinitrophenylhydrazones, m.p. 125°). The remaining material was repeatedly washed with soda in order to remove acid, and then the phenols were removed by means of 10% alkali. The phenolates were acidified with hydrochloric acid, the phenols extracted with ether, dried and distilled *in vacuo*. The yield of 3,4-dimethylphenol, with a m.p. of 62.5° (from petroleum ether) amounted to 8.6 g (64%). Xylenol was converted into 3-4-dimethylphenoxyacetic acid with a m.p. of 162° , which corresponds with the data in the literature [17].

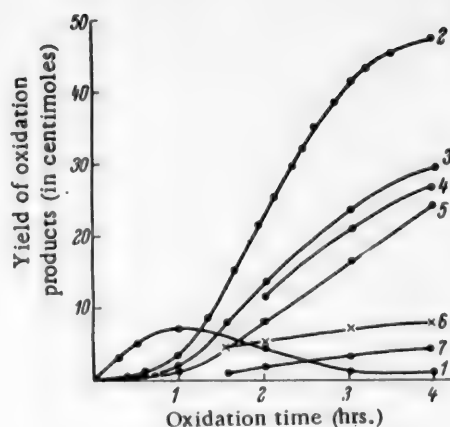


Fig. 3. Kinetics of the accumulation of the fundamental oxidation products of 4-isopropyl-o-xylene at 110°C and with an air flow of 1 liter/min in the presence of 170 mg-moles of cobalt acetate, 1) hydroperoxides; 2) water; 3) acids; 4) tertiary alcohols; 5) ketones; 6) primary alcohols; 7) lactones.

that this reaction is also characteristic for other derivatives of 3,3-dialkylphthalid. Derivatives of phthalid with substituents in the ring, as was pointed out above, are formed from hydroxyacids only in an acid medium, which permits the determination of the quantity of derivatives of 3,3-dialkylphthalid and phthalid in each others' presence.

SUMMARY

1. The auto-oxidation of 4-isopropyl-o-xylene and 3-isopropyl-o-xylene was studied. Conditions were found under which it is possible to oxidize them to a hydroperoxide concentration of 29 and 10%, respectively.
2. The oxidation products of 4-isopropyl-o-xylene were studied in detail.
3. It was found that on oxidizing 3-isopropyl-o-xylene, 3,3,7-trimethylphthalid is obtained in 40% yield along with the usual products.
4. A method was worked out for the analysis of lactones - derivatives of phthalid and 3,3-dialkylphthalid are simultaneously present in mixtures containing acids, esters and other compounds.

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The auto-oxidation of 3-isopropyl-o-xylene (II) and analysis of the reaction products were carried out analogously to compound (I). 15-18 g of hydrocarbon (II) were used for the reaction. The results of the experiments are given in the Table and in Fig. 1. The most characteristic aspect of this reaction was the formation of a lactone in comparatively high yield - 3,3,7-trimethylphthalid (III). The latter was separated from the reaction mixture by means of alkali, and also by distillation with subsequent freezing. Lactone (III) has a m.p. of 60.5° (from petroleum ether); it is soluble in alkali on heating but is insoluble in soda; on oxidation by alkaline permanganate it gave 3,3-dimethylphthalid-7-carboxylic acid (XII) with a m.p. of 185°. According to the literature [18], acid (XII) has a m.p. of 187°. Acid (XII) was also prepared by the oxidation of dimethyl- α -naphthylcarbinol [18] and was identical with that prepared by the oxidation of lactone (III). The cleavage of lactone (III) by heating with solid KOH resulted in the formation of acetone and o-toluic acid. The o-toluic acid has a m.p. of 105° and the acetone was identified as the 2,4-dinitrophenylhydrazone.

One of the properties of lactone (III) was used by us as a means of quantitatively determining this compound. If after the hydrolysis of lactone (III) the excess of alkali is very carefully titrated back, with cooling and using phenolphthalein, a certain fraction of the salt gives up alkali and is converted into lactone (III). By titrating back the alkali which is formed and heating the mixture once again, it is easy to convert all the salt into the lactone. Subsequently we found

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THE STABILITY OF THE 2,3-DIOXO- γ -LACTONE RING

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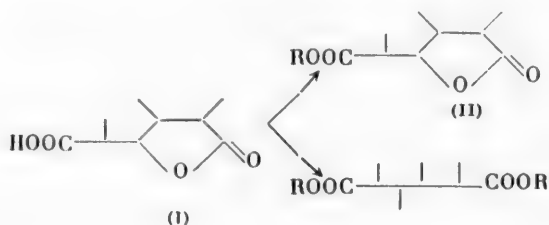
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It is customary to consider the acid-lactone equilibrium constant - the ratio of the rates of formation and hydrolysis of the lactone - as a criterion of the stability of the lactone ring. If one compares lactones with rings of various sizes, the largest values of this ratio are found among the γ -lactones. Substitution in the lactone ring has a considerable effect on the equilibrium point: alkyl groups as a rule increase the equilibrium constant, and this effect is strongly dependent on the place of substitution [1,2]. However the dependence of the stability of diastereoisomers of 2,3-dihydroxy-substituted γ -lactones on steric configurations has been very little studied up to the present time. According to the data of Levene and Simms [3], the rate of formation of all diastereoisomeric 2,3-dihydroxy- γ -lactones (and 2,3,4-trihydroxy- δ -lactones) of a given group (aldonolactones, monolactones of saccharodicarboxylic acids) are practically identical. Haworth and his co-workers [4], on the other hand, noted the marked dependence of the rate of hydrolysis of methylated γ - and δ -lactones of aldonic acids on configuration. As we discovered previously [5], the acid-lactone equilibrium constants for diastereoisomeric tetrahydroxyadipic acids at 18-20° fluctuates within the limits 1.55-0.40. The equilibrium constant, however, which only expresses the relative stability of the equilibrium components, is an absolutely basic criterion of the stability of the lactone ring, and under the best circumstances expresses only the thermodynamic stability of the lactone, which may not correspond with its stability under the conditions of this or that reaction: the direction of an irreversible process is determined only by its rate.

It appeared to be of interest to compare the stability of γ -lactones of some polyhydroxy- α , ω -dicarboxylic acids under proton-catalyzed esterification by a free (or lactonized) COOH group. This reaction is very characteristic for monolactones and for lactones in general and may serve as a criterion of the stability of the lactone ring under "dynamic" conditions - in case of the preservation of the lactone ring the reaction leads to the formation of a lactone ester, however if the ring is opened, a diester of polyhydroxycarboxylic acid is formed.



The few references in the literature that deal with the above-mentioned reaction point to the apparent dependence of the stability of the lactone ring on configuration. Hartmann obtained the diethyl ester of D-glycero-D-halo-(D- α -manno)-pentahydroxypimelic acid from syrupy lactonized acid* and ethanol by repeated evaporation. Zemlén, Mester and Móczár [8], on repeated evaporation of the monolactone of D-glycero-D-gulo-(D- α -gluco)-pentahydroxypimelic acid with ethanol and benzene, obtained the lactone ester. The lactone ring also was stable under re-esterification by propanol-1 and deacetylation of the tetraacetates of the lactone esters. On esterifying the 3,6-monolactone of D-glucosaccharic acid, Zinner and Fischer [9] obtained lactone esters with a yield of 69% (methanol) and 32% (ethanol). The monolactone of mucic acid on esterification by ethanol is converted into the dimethyl ester of mucic acid with a yield of 63% [10].

* The mutarotation of a solution of the acid indicates the formation of 1,4-lactone which has a more negative rotation [7].

Reaction products of the proton-catalyzed esterification of the COOH group of some mono- and dilactones of polyhydroxy- α , ω -dicarboxylic acids by means of methanol

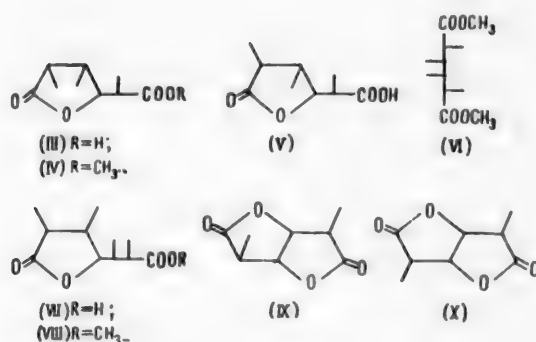
Lactone	Reaction product	Yield in %
3,6-Monolactone of D-glucosaccharic acid (I)	Lactone ester (II) (R = CH ₃)	60
1,4-Monolactone of D-talomucic acid (III)	Lactone ester ** (IV)	55
Monolactone of mucic acid (racemate) (V)	Diester (VI)	82
Monolactone of D-glycero-D-gulo-penta-hydroxypimelic acid (racemate) (VII)	Lactone ester ** (VIII)	60
D-Glucosaccharo-1,4,3,6-dilactone (IX)	1-Methyl ester of D-glucosaccharo-3,6-monolactone (II) (R = CH ₃)	53
D-Mannosaccharo-1,4,3,6-dilactone (X)	D-Mannosaccharo-1,4,3,6-dilactone (X)	56

* Obtained for the first time.

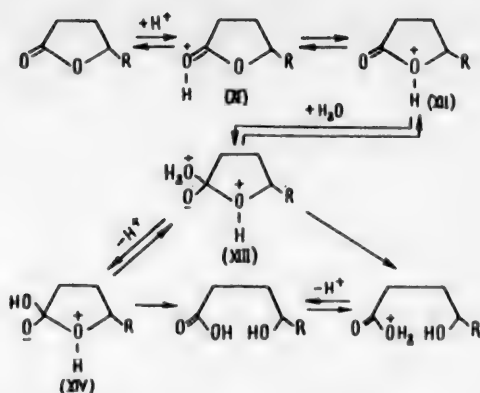
Preliminary experiments showed that the esterification of a free COOH group of monolactones by methanol in the presence of an activated cationite, while boiling or in the presence of dry hydrogen chloride at 0-10°, proceeds in only one direction. As a standard method we chose the esterification with methanol by boiling for six hours in the presence of cationite. The results obtained are shown in the table.

As can be seen from the data in the table, only those lactones are stable under the given conditions which have an OH group with identical configuration at carbon atoms 2 and 3, which is in accordance with the views of the authors mentioned above.

The result obtained with glucosaccharolactone cannot be considered to be entirely conclusive at the present time. The mutarotatory characteristics of syrupy 1,4,3,6-glucosaccharodilactone [11] and of crystalline 1,5,3,6-glucosaccharodilactone [11,12] are so close that there is some doubt as to their nonidentity (Fig. 1). At the same time the hydrolysis curves of both dilactones differ sharply from the hydrolysis curve of mannosaccharodilactone (Fig. 2) and are rather reminiscent of the behavior of δ -lactone. However, if the dilactone studied by us is indeed δ , γ -dilactone then the relatively easy opening of the δ -lactone ring while the γ -lactone ring is preserved would not occasion surprise.



The reasons for the difference in the stability of the diastereoisomeric 2,3-dihydroxy- γ -lactones is to be sought, apparently, in the mechanism of the reactions of esterification and hydrolysis and in the factors that facilitate them. The proton-catalyzed hydrolysis of lactones proceeds by the same mechanism as the hydrolysis of the majority of esters [13-16], namely, in accordance with the following scheme (some possible paths are shown):



The stability of the lactone group depends on: 1) the distribution of electron density between the ester and carbonyl oxygen atoms – the degree of interlinking of the p-electrons of the ester oxygen and the π -electrons of the CO group; 2) the internal (I-) linking [17], accompanying a change in the coordination number of the ester oxygen during the course of the reaction, and the addition of water or alcohol molecules to the C atom of the CO group. The first of these effects determines the rate of equilibrium of the addition of a proton and the ease of formation of the oxonium ions (XI) and (XII). In case the configuration of the 2,3-OH groups is identical, and H bond must exist between them and in consequence of this the degree of linking between them remains high* and only the addition of a proton to a carbonyl oxygen is possible; and the formation of (XII) and (XIII) becomes more difficult. The stability of the cyclic addition product (XII) or (XIV) is apparently of decisive significance for the course of the reaction since the decomposition of the latter is a stage that determines the rate of the entire reaction. Therefore one must assume that the configurational stability of cyclic structure (XIII) or (XIV) with unequal configuration of the 2,3-OH groups is considerably decreased, which is an immediate reason for the relatively easy opening of the ring. The formation of oxonium structures (XII-XIV) (but not XI) is connected with an increase of the Baierovskii linking in consequence of the deformation of the valence angles since the transition of the ester oxygen to oxonium must be accompanied by an increase in the valence angle C-O-C from 108-112 to 120°.

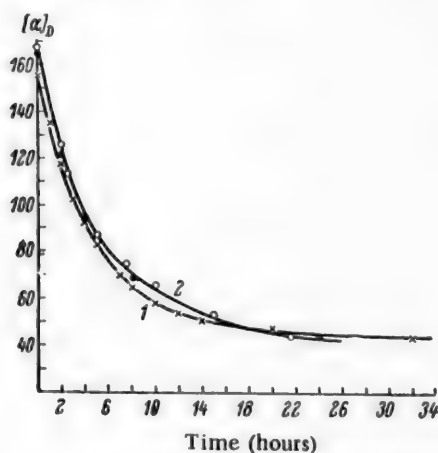
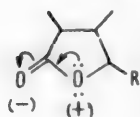


Fig. 1. Hydrolysis of γ,γ and δ,γ -dilactones of D-glucosaccharic acid (according to the data of [11,12]) 1) γ,γ -dilactone 2) δ,γ -dilactone

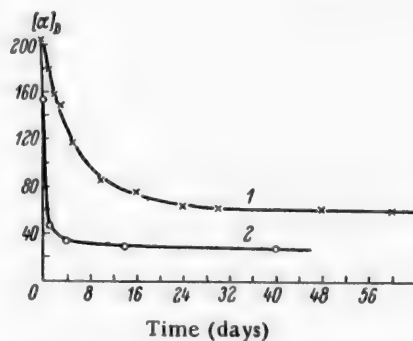


Fig. 2. Hydrolysis of γ,γ -dilactones of D-mannosaccharic and glucosaccharic acids. 1) D-mannosaccharodilactone; 2) D-glucosaccharodilactone [11].

It is interesting to note that the condition for the stability of the 2,3-dihydroxy- γ -lactone ring seems to be opposite the condition for the stability of the tetrahydropyran ring in accordance with the rule of Hassel and Ottar [18] by which, of

the two anomeric aldohexopyranosides the anomer with different (a, e) substituent bonds in positions 1,5 (1,3 in the case of aldopentopyranosides) has the greater stability.

* The high degree of linking must correspond to a high dipole moment and a high acidity of the monolactone ($R = \text{COOH}, -\text{CHOH}-\text{COOH}$).

EXPERIMENTAL

0.025 moles of lactone, 100 ml of methanol and 5 g of activated cationite* (Vofatit F) were boiled for six hours in a flask with a reflux condenser on a water bath. The cationite was filtered off, washed with methanol and the filtrate evaporated under vacuum to a syrupy consistency which crystallized in the desiccator in the cold; the crystalline material was washed with ether and recrystallized.

The 1-methyl ester of the 3,6-monolactone of D-glucosaccharic acid (II). M.p. 151-153° (from a mixture of methanol and ether). The literature shows: m. p. 113-114° [19], 156° [9].

Found %: C 40.98; H 4.84; OCH₃ 14.8. C₇H₁₀O₇. Calculated %: C 40.78; H 4.89; OCH₃ 15.05.

The 6-methyl ester of the 1,4-monolactone of D-talomucic acid (IV). M.p. 198-201° (from a mixture of methanol and ether).

Found %: C 40.92; H 4.80; OCH₃ 15.2. C₇H₁₀O₇. Calculated %: C 40.78; H 4.89; OCH₃ 15.05. [20], 167° [21], 196-198° (decomp.) [22].

The methyl ester of the DL-monolactone of D-glycero-D-gulopentahydroxy-pimelic acid (VIII). M.p. 188-189 (from methanol).

Found %: C 40.74; H 5.16; OCH₃ 13.3. C₈H₁₂O₈. Calculated %: C 40.68; H 5.12; OCH₃ 13.14.

The dimethyl ester of mucic acid (VI). M.p. 192-194° (decomp.) (from methanol). The literature gives: M.p. 205° (decomp.) [20], 167° [21], 196-198° (decomp.) [22].

Found %: C 40.26; H 5.98; OCH₃ 25.7. C₈H₁₄O₈. Calculated %: C 40.34; H 5.92; OCH₃ 26.06.

SUMMARY

1. The stability of the γ -lactone ring of the 3,6-monolactone of D-glucosaccharic acid, of the 1-4-monolactone of D-talomucic acid, of the DL-monolactone of mucic acid, of the DL-monolactone of D-glycero-D-gulopentahydroxypimelic acid and of the 1,4,3,6-dilactones of D-glucosaccharic and mannosaccharic acids during proton-catalyzed esterification of the COOH group was studied.

2. Under the conditions of this reaction, the identical configuration of the OH groups at carbons 2 and 3 stabilizes the lactone ring.

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*The cationite was activated in an ion-exchange column by treatment with 3 N HCl, then washing with water until it gave a neutral reaction with bromthymol blue, and drying in vacuo.

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KINETICS OF THE LACTONIZATION OF DIASTEREOISOMERIC TETRAHYDROXYADIPIC ACIDS

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In previous papers [1,2], by using polarimetric measurements, we studied the kinetics of the formation and hydrolysis of the lactones of diastereoisomeric tetrahydroxyadipic acids. It was found that talomucic, mannosaccharic and idosaccharic acids at 18-20°, form lactones at approximately the same rate, differing noticeably only from glucosaccharic acid which forms a lactone from 3-5 times faster.

In the present paper we present the results of a study of the kinetics of lactone formation of all the tetrahydroxyadipic acids (with the exception of allomucic acid) at 40 and 60°, which we obtained by means of titration.

In 1896 Hjelt [3] found that mucic acid at 52° forms a lactone considerably faster than D-glucosaccharic acid. According to the data of Leven and Simms [4], however, mucic, DL-talomucic*, D-glucosaccharic and D-mannosaccharic** acids at 40° form lactones at practically the same rate which is somewhat less than the rate of formation of γ -lactones by aldonic acids. The constants of the rates of reaction were not calculated since the results of the titrations were not entirely satisfactory.

The results of our determination indicate that the rates of lactone formation of diastereoisomeric tetrahydroxyadipic acids at 40 and 60° differ noticeably from one another; with increasing temperature these differences become even more noticeable. Lactone formation in all cases proceeds as a first-order reaction. The constants of the rates of reaction increase in the series: manno < gluco < ido < talo. The same sequence occurs in the temperature coefficients of the reaction (2.63-3.53). The values of the rate constant (k), the activation energy (E^*) and the logarithm of the pre-exponent (of the frequency index $A = \lg \alpha$, $k = \alpha e^{-E^*/RT}$) are shown in the table.

Basic data on the kinetics of lactone formation of diastereoisomeric tetrahydroxyadipic acids

Acid	$k \cdot 10^4$ per hr		E^* cal/mole	A for α [sec ⁻¹]
	40°	60°		
D-Mannosaccharic . . .	61	420	19.6	7.9
D-Idosaccharic	85	833	23.1	10.5
D-Glucosaccharic . . .	73	601	21.4	9.2
D-Talomucic	108	1345	25.6	12.3
Mucic	96	1182	25.4	12.2

The activation energy was calculated without taking into account the viscosity of the solution; when it is, the values of E^* shown in the table are increased by 3.4 Cal (activation energy due to viscosity).

The constants of the rate of lactone formation of diastereoisomeric acids at 20°, calculated by means of the values of the activation energy shown, are less than those previously found by us by the polarimetric method [1,2] by

*Erroneously called allomucic acid by them [5].

**Glucosaccharic and mannosaccharic acids had not yet been obtained in crystalline form at that time.

47-61% and in the case of glucosaccharic acid only - by 88%. These deviations are apparently due to a defect in the methods (each of these methods is completely different; the activation energies were calculated from the rate constant for only two temperatures).

The kinetics of the formation and hydrolysis of the 3,6-monolactone of D-glucosaccharic acid was studied long ago by Meyer [6] by the polarimetric method at 18 and 25.2°. The energy of activation of lactone formation of glucosaccharic acid, calculated by us from his data, amounts to 19.7 Cal/mole, deviating from the value found by us by 7.6%. It is necessary to take into account the fact that the precision of the determination of the energy of activation rarely exceeds ± 1 Cal [7], which corresponds to a relative error of the order of 4-10%.

Differences in the pre-exponent (frequency factor) of the Arrhenius equation for the lactone formation of tetrahydroxyadipic acids are of very great interest. Taking into consideration the degree of precision of determination $A \pm 0.7 - 0.8$ [7], the differences found for one and the same type of reaction of the diastereoisomers are very significant and require explanation. The value of A for the lactone formation of glucosaccharic acid, calculated by us from Meyer's data [6], is equal to 8.8, which agrees well with the value which we found.

The frequency factor of monomolecular reactions, as is well-known, usually has the order of magnitude of its own atomic vibrations at a broken bond, i.e., about 10^{13} sec^{-1} [8].

$$\nu = \frac{kT}{h}$$

k - Boltzmann constant; h - Planck constant

Sharply decreased values of the pre-exponent for a monomolecular reaction are found when the reaction is non-adiabatic (from the point of view of quantum mechanics) [9], for example in the case of some cis-trans isomerizations and also during the formation of cyclic end products or intermediate products or a transitional complex* [7]. The magnitude of the probability factor of the cyclization reaction is determined by the frequency of the conformation of the hydrocarbon chain which is favorable to the closing of the ring and by the distance between the reaction centers, i.e., by the size of the ring formed [7, 10-13]. Thus, for example, the frequency factor for the cyclization of ω -bromo-n-alkylamines to the corresponding cyclopolymethyleneimines varies within the limits 11-15 [10]. The rate of cyclization is a function of the distance between the reaction centers, of the frequency which is favorable to a cyclic conformation of the chain, and of the tension in the ring that is formed. As a result of the "intersection" of these factors which change antipatically, a five-membered ring usually has the maximum rate of formation [10-13].

The rate constant of the monomolecular reaction

$$k_1 = \frac{kT}{h} e^{\frac{\Delta S^*}{R}} e^{-\frac{\Delta H^*}{RT}}$$

(where: ΔS^* is the entropy of activation; ΔH^* is the heat of activation; for reactions in solutions $\Delta H^* = E^* - RT$ and for temperatures which are not very high $\Delta H^* \approx E^*$) is the product of three factors: the normal frequency factor ($\approx 10^{13}$), the entropy factor which is characteristic of the height of the entropy barrier of the reaction (probability of achieving a transitional state) and the enthalpy factor which is characteristic of the energy of the transitional state, i.e., the energy barrier of the reaction [14]. The activation energy of the cyclization reaction may be presented as the sum [15] of at least four components: 1) the energy expended in moving the reacting groups close together and the formation of the optimum conformation (E_{sb}); 2) the energy required to overcome the classical (barrier) tension resulting from the deformation of the optimum valence angles in the cycle which is formed (E_a); 3) the energy connected with the occurrence of unfavorable conformation of the ring (conformational, non-classical tension) (E_k); 4) the activation energy of the reaction itself (E_0) which is identical for all cyclizations of a given type (dehydration, dehydrochlorination, etc.).

$$E^* = E_{sb} + E_a + E_k + E_0.$$

* The formation of the ring is connected with losses of entropy in consequence of the transfer of the energy of internal rotation to vibrational energy.



Fig. 1. "Lactone-forming" conformation of a hydrocarbon chain of 6 C-atoms (mirror image forms are not shown)

hydroxyadipic acids, there are eight that have coplanar conformations that easily change from one to another by the rotation of one or both of the terminal chains (Fig. 1).*

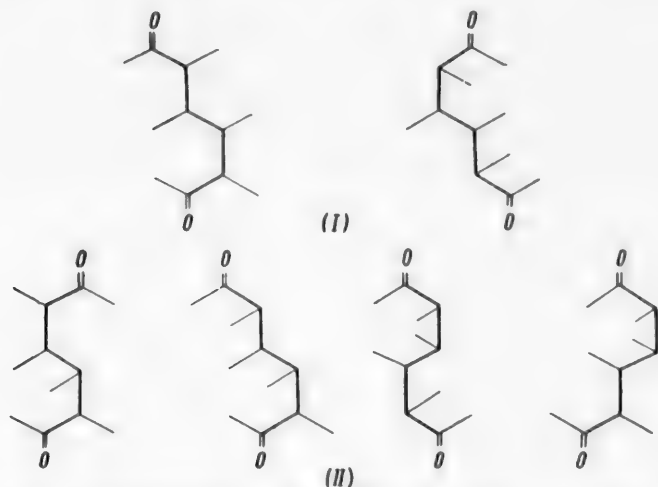


Fig. 2. Conformations of the hydrocarbon chain of D-glucosaccharic (I) and D-talomucic (II) acids which are favorable to the formation of γ -lactones.

Inasmuch as, in the case of the formation of slightly strained γ -lactone rings by diastereoisomeric acids, the magnitudes of E_A and E_O may be considered correspondingly identical, the differences in the lactonization constants of these acids may be caused only by differences in the magnitudes of the entropy factors and the energy components E_{SB} and E_K which depend on the steric configuration of the chain. Comparison of the rate constants k_A, k_B of two diastereoisomers A, B results in the expression:

$$\ln \frac{k_A}{k_B} = \frac{\Delta S_A^* - \Delta S_B^*}{R} - \frac{E_{SB}^A - E_{SB}^B + E_K^A - E_K^B}{RT}$$

Differences in the magnitudes of the entropy factor obviously lead to differences in the position of statistical equilibrium of conformations of the hydrocarbon chain which are favorable and unfavorable for cyclization. The position of this equilibrium may be evaluated on the basis of the following considerations. Among all the possible conformations of the ring of tetra-

If only those conformations which correspond with (precede) the existence and separation of γ -lactones (the formation of δ -lactones of tetrahydroxyadipic acids may be excluded on the basis of the kinetic picture of lactonization) are considered favorable for ring formation, then it appears that the number of favorable conformations (n_L) amounts to 1 for mannosaccharic acid (dilactone), to 3 for idosaccharic acid (monolactone and dilactone) [16], to 2 for glucosaccharic acid, and to 4 for talomucic, mucic and allomucic acids. Lactone-forming conformations of the ring of D-glucosaccharic and D-talomucic acids are shown in Figure 2.

Comparison of the statistical weight (in the sense of the apriori probability of the state) W ($+ n_L/8$) of favorable conformations and the magnitude of the frequency index show that the function $A = f(\lg W)$, within the limits of precision of determining A , is linear (Fig. 3):

$$A = a + b \lg W,$$

where $a = 14$, $b = 7$ and, consequently, if $a = \lg \nu = 14$,

$$\Delta S^* = c \lg W$$

($c = 2.303 bR$). Since $\lg W < 0$, ΔS^* represents negative values as is usually the case in reactions with a transitional ring state or reaction product [7] if $\alpha = 10^{13}$, $\Delta S^* = 0$).

*In this connection we only take into consideration unfolded conformations of the hydrocarbon chain and those conformations in which closing of a 5-membered ring by the participation of $C(1)$ or $C(6)$, which corresponds with two internal vibrational degrees of freedom (only the conformations indicated are of interest in the case of acid-lactone conversions of tetrahydroxyadipic acids). Comparison of identical conformations of different diastereoisomers is based on the plausible assumption that the number of degrees of freedom and the statistical weight (importance) of all the corresponding conformations for all the stereoisomers of a given group are identical.

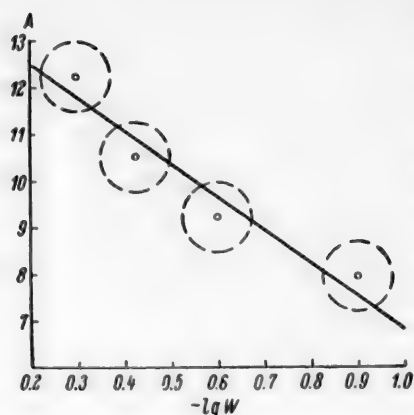
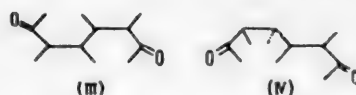


Fig. 3. Dependence of the frequency index (A) of the Arrhenius equation for the lactonization of tetrahydroxyadipic acids on the probability state (W) of the conformation of the hydrocarbon chain favorable to ring formation (the limits of error are designated by circles).

in the probability factor and the activation energy is apparently extremely common in the kinetics of monomolecular reactions.

The most significant loss of entropy occurs in the lactonization of mannosaccharic acid which, apparently, is connected with the formation of a dilactone of bicyclic conformation.

However, differences in the magnitudes of activation energy, in our opinion, may be explained by the steric effect of the OH groups that form the lactone ring. These OH groups may hinder the moving together of the reaction centers preceding the closing of the ring, or even inhibit the splitting off of a molecule of water. Thus, for example, the closing of the lactone rings in the case of mannosaccharic acid (III) occurs in a "reaction space" that is free of OH groups, while in the case of talomucic acid (IV) this is blocked by OH groups to a considerable degree.



In order for this reaction to occur, it requires supplementary activation energy in order to overcome steric hindrance — the "removal" of the screening substituent etc. [17]; this energy corresponds to that of components E_{sb} and E_K . It is significant that the activation energy increases in the series manno < gluco < ido < halo < talo, parallel with the degree of filling of the intramolecular space by OH groups [18]. The symbatic character of the change

EXPERIMENTAL

The rate constants of lactone formation were determined by the usual methods [3,4,19,20]. Solutions of the acids had a concentration of 0.03 M. The length of heating at the temperature of the experiment varied from 30 minutes to 96 hours. After cooling with ice, the samples were titrated with 0.02 N NaOH, free from CO_2 , in the presence of phenolphthalein. The rate constants were calculated according to the formula

$$k = \frac{2.303}{t} \lg \frac{a}{a-x},$$

where: a — is the initial concentration of acid, and x is the decrease in concentration in time t . The values of the constants shown in the table are the averages of 5-6 measurements. The error of k varies within the limits $\pm 5/20\%$, or $\pm 15\%$ on the average.

SUMMARY

1. By means of titration the constants of the rate of lactone formation of all diastereoisomeric tetrahydroxyadipic acids (with the exception of allomucic acid) were determined at 40 and 60°. The values of the activation energy and the frequency factor were calculated.

2. The values of the constants of the rate of lactone formation, of the energy of activation and of the pre-exponent increase in the series: manno < gluco < ido < halo \leq talo.

3. Differences in the magnitude of the frequency factor may be explained by the different statistical weight (probability of the state) of the conformations of the carbon chain which are favorable to cyclization.

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SYNTHESES IN A SERIES OF ISOXANTHINE DERIVATIVES

VI. HALOGEN DERIVATIVES OF (ISOCAFFEINE-8)-MALONIC ESTER

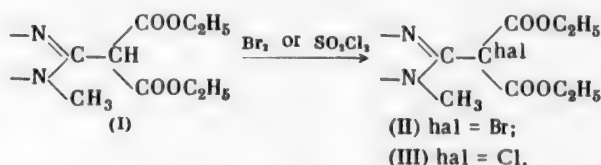
E. S. Chaman and E. S. Golovchinskaya

S. Ordzhonikidze All-Union Chemico-Pharmaceutical Institute for Scientific Research

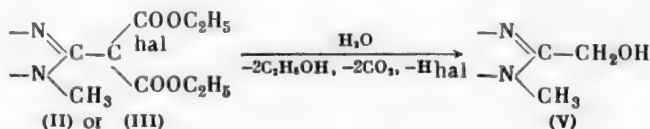
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 8,

pp. 2645-2650, August, 1961

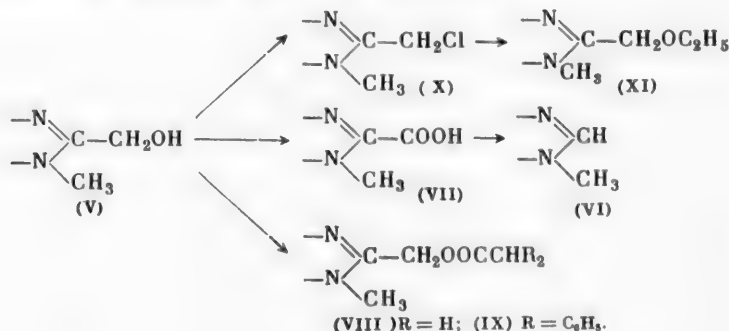
A study of the halogenation of (isocaffeine-8)-malonic ester, described in a previous paper[1], resulted in the formation of bromo- and chloro- derivatives of this ester. (Isocaffeine-8)-bromomalononic ester (II) was obtained from the reaction of the diester (I) with bromine; the corresponding chloromalononic ester (III) was formed by the action of sulfuryl chloride on (I).



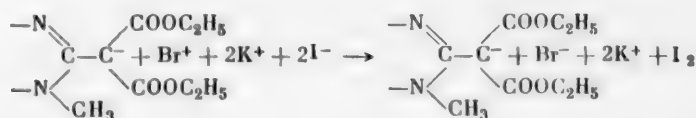
On heating the halogen derivatives of isocaffeinemalonic ester (II) and (III) with dilute mineral acid, a hydrolytic cleavage of both carboethoxyl groups occurred, analogous to that described for the unhalogenated isocaffeine-malonic ester (I) [1], and also for (caffeine-8)-malonic ester (IV) which is isomeric with it [2]. As might be expected, the halogen linked to the malonic group underwent hydrolysis simultaneously, as a result of which the product of the reaction was 8-hydroxymethylisocaffeine (V) which was previously unknown.



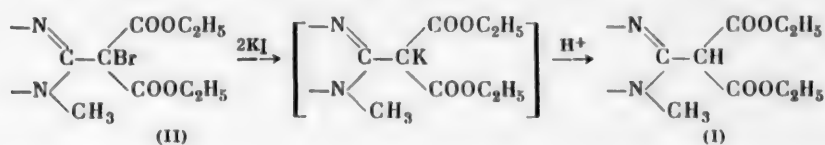
Its structure was confirmed by a series of reactions: by the preparation of isocaffeine (VI) by oxidation and subsequent decarboxylation of the intermediate isocaffeine-8-carboxylic acid (VII), by the formation of the esters (VIII) and (IX), by reaction with thionylchloride which led to the formation of 8-chloromethylisocaffeine (X) and, finally, by the conversion of the latter into 8-ethoxymethylisocaffeine (XI).



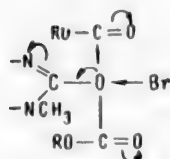
During the course of further work with (isocaffeine-8)-halomalonic esters (II) and (III) it was found that the halogen in them in many reactions shows the properties of positively charged halogen. The ability of halogen to react as a cation is shown particularly clearly in the case of (isocaffeine-8)-bromomalonic ester (II), which even in the absence of mineral acid clearly shows a so-called "ionic reaction", i.e., it oxidizes KI in aqueous solution with the formation of two equivalents of iodine.



After completion of the separation of I_2 from KI, it is possible to extract debrominated diester (I) from the solution which has been back-titrated with thiosulfate and acidified.

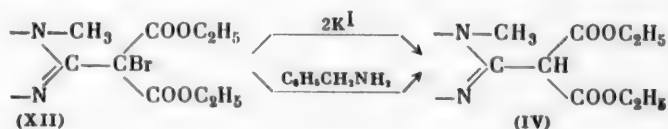


The ability of bromine in bromomalonic ester and its derivatives to dissociate as a cation in some reactions - despite the fact that the affinity of bromine for electrons is somewhat greater than that of carbon - has long been known [3]. In the present study it was found that this peculiarity of bromomalonic ester, which is the result of the influence of two carboethoxyl groups at the C-Br bond, is further strengthened in compounds (II) and (III) by the neighboring isocaffeine residue. Since it is bound by its C_8 atom to malonic ester, it apparently plays the role of a third electron acceptor group and assists in drawing the generalized electron pair from an atom of bromine to the atom of carbon which is joined to it.



This property of the isocaffeine molecule as an electronegative group in relation to its substituents at position 8 has a close analogy and therefore is not unexpected. The views given above correspond completely with the previously discovered facts on the peculiar influence of the caffeine ring on the course of a number of processes in the malonic residue of (caffeine-8)-malonic ester (for example its cleavage in the presence of alcoholates [2]). These earlier data have been supplemented in the present research by the synthesis and study of the reactions of (caffeine-8)-bromomalonic ester (XII) and (caffeine-8-chloromalonic ester (XIII) - compounds which are isomeric with (isocaffeine-8)-halomalonic esters (II) and (III) and differ from the

latter only by a different location of the double bonds and, consequently, of the CH_3 group in the imidazole part of the molecule of methylated 2,6-dihydroxypurine ($\Delta^{8,9}$ instead of $\Delta^{7,8}$). It was shown that the behavior of (isocaffeine-8)- and (caffeine-8)-halomalonic esters is completely analogous and that in particular, (caffeine-8)-halomalonic esters from I_2 as easily as their isocaffeine isomers on reacting with a solution of KI. Halogen is also reduced in them during attempts at condensation with benzylamine, while in both cases dehalogenated (caffeine-8)-malonic ester (IV) may be separated from the reaction mixture.



The diesters (XII) and (XIII), as a result of hydrolysis in the presence of mineral acids, are converted into 8-hydroxymethylcaffeine (XIV) which is identical with the 8-hydroxymethylcaffeine previously synthesized by one of us [4]. In other words, under these conditions the usual hydrolytic cleavage of halogen takes place and it is replaced

by a hydroxyl group*, i.e., in this case also the reaction proceeds in exactly the same way as the corresponding reactions of the (isocaffeine-8)-halomalonic esters.

EXPERIMENTAL

(Isocaffeine-8)-bromomalonic ester (II). A solution of 2.5 g of Br_2 in 10 ml of CHCl_3 is added drop by drop to a solution of 5 g of (isocaffeine-8)-malonic ester (I) in 40 ml of dry CHCl_3 at 20° . This is stirred for 20 minutes and boiled for four hours. The thick suspension of crystals of the dihydrobromide of (isocaffeine-8)-bromomalonic ester which are red in color** is mixed with 50 ml of a 5% solution of NaHCO_3 ; the chloroform layer is separated, washed with water, and dried over Na_2SO_4 . The CHCl_3 is distilled off in vacuo and the remaining material is triturated with 15 ml of ethyl acetate and the (isocaffeine-8)-bromomalonic ester (II) is separated; yield 5.14 g (84%), m.p. $168-170^\circ$ (decomp.). For analysis it was crystallized from ethyl acetate, m.p. $170-172^\circ$ (decomp.).

Found %: N 12.78; Br 18.37. $\text{C}_{15}\text{H}_{19}\text{O}_6\text{N}_4\text{Br}$. Calculated %: N 12.99; Br 18.54.

Titration of (isocaffeine-8)-bromomalonic ester. An aqueous solution of 1 g of KI was added to a suspension of 0.3350 g of (II) in 50 ml of 45% alcohol. The mixture was allowed to stand in the dark for four hours with periodic stirring; then the iodine that separated was titrated. 13.5 ml of 0.1 N $\text{Na}_2\text{S}_2\text{O}_3$ were required; calculated: 15.54 ml. The titrated solution was acidified and extracted with chloroform which yielded 0.15 g of (isocaffeine-8)-malonic ester (I) with a m.p. of $138-139^\circ$. The temperature of a mixed melting point test with (I) [1] was $138-139^\circ$.

(Isocaffeine-8)-chloromalonic ester (III). A solution of 5 ml of SO_2Cl_2 in 10 ml of CHCl_3 was added to a solution of 5 g of (I) in 30 ml of dry CHCl_3 . The mixture was allowed to stand for 12-15 hours at 20° , after which it was washed with water and a solution of NaHCO_3 , dried over Na_2SO_4 and the solvent evaporated to dryness in vacuo. By stirring the residue with 10-15 ml of ethyl acetate (isocaffeine-8)-chloromalonic ester (III) was obtained. Yield 4.5 g (82%); for analysis it was crystallized from ethyl acetate, m.p. $207-208^\circ$ (decomp.).

Found %: Cl 9.26. $\text{C}_{15}\text{H}_{19}\text{O}_6\text{N}_4\text{Cl}$. Calculated %: Cl 9.18.

If the reaction of (I) with SO_2Cl_2 takes place during 3-4 hours of boiling, the yield of (III) is somewhat decreased (to 75-76%). In this case the formation of a second substance is observed which does not contain chlorine and has a m.p. of $183-185^\circ$; its structure has not yet been determined. This substance, which may be titrated with 0.1 N NaOH and phenolphthalein, may be separated from the reaction mixture in a 5-8% yield as follows: 80-90% of the solvent is distilled from the chloroform solution obtained after the completion of the reaction which has been washed and dried as described above; ethyl acetate is added to the thick residue and compound (III) which separates, is removed by filtration. Coarse crystals slowly form in the thickened filtrate on standing and for analysis are recrystallized from dichloroethane.

Found %: C 42.48; H 4.61; N 23.79.

8-Hydroxymethylisocaffeine (V). 23 g of (isocaffeine-8)-chloromalonic ester (III) was boiled with 400 ml of dilute hydrochloric acid (1 : 1) for 3-4 hours until solution was complete. The solution was treated with carbon, filtered and evaporated to dryness in vacuo. The remaining HCl was carefully removed by twice adding water in 30-50 ml quantities. The dry material that remained was stirred with 120-150 ml of anhydrous alcohol and $\text{N}(\text{C}_2\text{H}_5)_3$ added until the reaction was neutral (pH 7). This was then cooled, the crystals of 8-hydroxymethylisocaffeine (V) were separated, washed with alcohol, boiled with 100-150 ml of CHCl_3 and the hot suspension filtered. The weight of the residue was 11 g (81%). For analysis it was crystallized from CHCl_3 1 : 1300; m.p. $253-255^\circ$. Solubility: in boiling alcohol 1 : 120; in water at 100° 1 : 7, at 20° 1 : 30.

In a similar manner 1.3 g (50%) of 8-hydroxymethylisocaffeine with a m.p. of $245-248^\circ$ was obtained from 5 g of (isocaffeine-8)-bromomalonic ester (II).

Found %: C 48.42; H 5.41; N 24.62. $\text{C}_9\text{H}_{12}\text{O}_3\text{N}_4$. Calculated %: C 48.21; H 5.39; N 24.91.

* It is entirely probable that hydrolytic cleavage of halogen in (isocaffeine-8)- and (caffeine-8)-halomalonic esters takes place only after the cleavage of one or even of both carboethoxyl groups.

** Determination of bromine by various methods in a sample of the filtered crystals gave the following results: a) According to Stepanov. Found %: Br 40.85. b) By titration with KI in acid solution. Found %: Br^+ 13.47. c) By titration according to Folgarty in 10% HNO_3 . Found %: Br^- 27.40. $\text{C}_{15}\text{H}_{19}\text{O}_6\text{N}_4\text{Br} \cdot 2\text{HBr}$. Calculated %: total Br 40.48; Br^+ 13.49; Br^- 26.96.

The oxidation of 8-hydroxymethylisocaffeine. 20 ml of a 5% solution of KMnO_4 was added drop by drop at 40-42° to a solution of 1 g of (V) in 50 ml of water over a period of 25-30 minutes. This was filtered, the filtrate acidified (pH 6), evaporated to a volume of 10-15 ml *in vacuo* and then cooled. The crystals of (isocaffeine-8)-carboxylic acid (VII) that formed were separated, dissolved in a solution of NaHCO_3 , with evolution of CO_2 , and precipitated from the solution by acidification. The weight was 0.5 g; m.p. 250-260°. The crystals obtained were boiled for two hours with 3 ml of water until evolution of CO_2 ceased; isocaffeine (VI) crystallized from the chilled solution. Its weight was 0.18 g, m.p. 270-272°. A mixed melting point test with isocaffeine [5] showed 274-276°.

8-Acetoxyethylisocaffeine (VIII). 1 g of compound (V) was boiled for one hour with 5 ml of acetic anhydride. The acetic anhydride was distilled off *in vacuo*, the residue dissolved in water and neutralized (pH 7). 0.85 g of 8-acetoxyethylisocaffeine (VIII) was obtained. After being twice recrystallized from alcohol (1:15) the m.p. was 169-171°.

Found %: C 49.89; H 5.26; N 21.20. $\text{C}_{11}\text{H}_{14}\text{O}_4\text{N}_4$. Calculated %: C 49.62; H 5.29; N 21.05.

8-Diphenylacetoxyethylisocaffeine (IX). 0.75 g of compound (V), 1 g of the chloride of diphenylacetic acid and 0.5 g of pyridine were boiled in 30 ml of anhydrous benzene for three hours. The benzene was distilled off *in vacuo* and the remaining material repeatedly washed with water and a solution of NaHCO_3 . 1.4 g of crystals was obtained with a m.p. of 223-225°; after crystallization from dimethylformamide (1:7) the m.p. was 225-226°.

Found %: N 13.24. $\text{C}_{23}\text{H}_{22}\text{O}_4\text{N}_4$. Calculated %: N 13.38.

8-Chloromethylisocaffeine (X). 7 ml of SOCl_2 were added to 5.5 g of compound (V) in 20 ml of anhydrous CHCl_3 with external cooling; then the mixture was slowly heated and stirred for four hours at the boiling point. The CHCl_3 and the excess SOCl_2 were distilled off and the remaining material stirred with 15 ml of ice water and neutralized with dry NaHCO_3 (pH 6-7). The filtered precipitate of 8-chloromethylisocaffeine (X) was washed with water; its weight was 5.1 g (85%). For analysis it was crystallized from dichloroethane (1:12). On rapid heating the compound decomposes at 185-185.5°; when slowly heated it gradually decomposes, after which it does not melt up to 310°.

Found %: Cl 14.63. $\text{C}_9\text{H}_{10}\text{N}_4\text{Cl}$. Calculated %: Cl 14.62.

0.5157 g of 8-chloromethylisocaffeine (X) was boiled with 20 ml of water for four hours. The solution was titrated with alkali. 20.75 ml of 0.1 N NaOH were required; calculated 21.2 ml. The neutral solution was evaporated to dryness and, by stirring with 8 ml of 50% alcohol, 0.25 g of compound (V), m.p. 243-244°, was obtained.

8-Ethoxymethylisocaffeine (XI). 1.8 g of (X) was heated for three hours with a solution of NaOC_2H_5 in 10 ml of alcohol (from 0.17 g of Na). The alcohol was distilled off *in vacuo*, the remaining material extracted with CHCl_3 , the solution dried and the solvent distilled off. After crystallizing the residue from ethyl acetate (1:15), 0.75 g of purified 8-ethoxymethylisocaffeine (XI), m.p. 153-155°, was obtained.

Found %: N 22.13. $\text{C}_{11}\text{H}_{16}\text{O}_3\text{N}_4$. Calculated %: N 22.20.

(Caffeine-8)-bromomalononic ester (XII). A solution of 5.7 g of bromine in 10 ml of CHCl_3 was added at 20° to a solution of 13.4 g of (caffeine-8)-malonic ester (IV) in 100 ml of dry CHCl_3 and the mixture stirred for two hours at 70-85°. At first a reddish precipitate formed which gradually dissolved. The solution was washed with solutions of NaHSO_3 and NaHCO_3 and then with water, dried over Na_2SO_4 and the CHCl_3 distilled off *in vacuo*. The remaining material was stirred with 20 ml of ether and filtered. 10.2 g of (caffeine-8)-bromomalononic ester (XII) with an m.p. of 154-158° were obtained, which was crystallized for analysis from ethyl acetate (1:4). An additional 4 g of impure material crystallized from the ether solution. The total yield of purified (XII) was 13.2 g (80%), m.p. 162-164°.

Found %: Br 18.52; N 13.05. $\text{C}_{16}\text{H}_{19}\text{O}_6\text{N}_4\text{Br}$. Calculated %: Br 18.54; N 12.99.

Titration of (caffeine-8)-bromomalononic ester. a) In neutral solution. A solution of 1 g of KI was added to a suspension of 0.2303 g of (XII) in 50 ml of 45% alcohol which was then kept in the dark for four hours with periodic stirring; then the iodine that was formed was titrated. 9.65 ml of 0.1 N $\text{Na}_2\text{S}_2\text{O}_3$ were required; calculated 10.68 ml. After acidification of the titrated solution, (caffeine-8)-malonic ester (IV) with a m.p. of 154-157° was extracted from it with chloroform. A mixed melting point test with a known sample of compound (IV) [2] showed 155-157°.

b) In acid solution. 10 ml of a 10% H_2SO_4 was poured into a suspension of 0.2049 g of (XII) in 50 ml of 45% alcohol, and 1 g of KI was added. It was titrated within four hours and 9.55 ml of 0.1 N $\text{Na}_2\text{S}_2\text{O}_3$ were required; calculated 9.51 ml. Compound (IV), m.p. 154-156°, was extracted from the solution.

Hydrolysis of (caffeine-8)-bromomalononic ester. 3 g of (XII) in 60 ml of 20% HCl was boiled for four hours, the solution evaporated to dryness *in vacuo*, traces of acid removed with water, the residue stirred with 10-15 ml of water and 0.5 g of crystals of 8-bromomethylcaffeine separated. After crystallizing from alcohol the m. p. was 206-208°. The temperature of a mixed melting point test with 8-bromomethylcaffeine [4] was 207-208°. The filtrate obtained after separation of the 8-bromomethylcaffeine was again evaporated *in vacuo*, the residue stirred with 10 ml of alcohol and neutralized with $N(C_2H_5)_3$ (pH 6-7). The 8-hydroxymethylcaffeine filtered off was crystallized from alcohol. Yield 0.72 g, m.p. 222-225°. The temperature of a mixed melting point test with hydroxymethylcaffeine [4] was 223-225°.

The reaction of (caffeine-8)-bromomalononic ester (XII) with benzylamine. 4.2 g of (XII) and 2.7 ml of benzylamine were boiled for four hours in 40 ml of dry benzene and were filtered after cooling. The weight of the benzylamine hydrobromide obtained was 0.75 g, m.p. 213-216°. The temperature of a mixed melting point test with benzylamine hydrobromide [6] was 213-216°. The benzene was distilled off *in vacuo*, and the remaining material dissolved in ether. Within 48 hours the crystals that form (2 g) were separated, carefully washed with water and crystallized from ethyl acetate. 0.8 g of the original (XII) gradually crystallized out, while impure (caffeine-8)-malonic ester (IV) with an m.p. of 130-154° was separated from the filtrate after evaporation to dryness. After crystallization from alcohol this melted at 153-155°; its weight was 0.46 g. Another 0.38 g of (IV) was separated from the wash water by extraction with chloroform. The ether mother solution was evaporated to dryness. On treating the residue with dilute HCl a distinct smell of benzaldehyde was observed.

(Caffeine-8)-chloromalononic ester (XIII). 3 ml of SO_2Cl_2 in 7 ml of $CHCl_3$ was added to a solution of 10.65 g of (caffeine-8)-malonic ester (IV) in 50 ml of anhydrous $CHCl_3$ and the mixture boiled for five hours. Then it was evaporated to dryness *in vacuo*, the residue dissolved in 30 ml of $CHCl_3$, the solution washed with a solution of $NaHCO_3$ and water, dried over Na_2SO_4 , the chloroform distilled off and the residue stirred with ethyl acetate. (Caffeine-8)-chloromalononic ester (XIII) with a m.p. of 139-140° was obtained. Yield 11.4 g (73%); after crystallization from 35 ml of ethyl acetate the m.p. was 141-142°.

Found %: Cl 9.28. $C_{15}H_{19}O_6N_4Cl$. Calculated %: Cl 9.18.

Hydrolysis of (caffeine-8)-chloromalononic ester. 0.4 g of (XIII) was boiled for four hours with 10 ml of 20% HCl, the solution evaporated *in vacuo*, the residue stirred with 1-2 ml of water and neutralized with a solution of $NaHCO_3$ (pH 6-7). 0.15 g (70%) of 8-hydroxymethylcaffeine with an m.p. of 214-222° was obtained by crystallizing from water. The temperature of a mixed melting point test with 8-hydroxymethylcaffeine [4] was 220-225°.

SUMMARY

1. By brominating (isocaffeine-8)- and (caffeine-8)-malonic esters, their bromo- and chloro- derivatives were prepared. The halogen contained in these compounds has the ability to react as positively charged halogen.
2. (Isocaffeine-8)-halomalononic esters were converted by hydrolysis into 8-hydroxymethylisocaffeine from which its ethers and esters and also 8-chloromethylisocaffeine were obtained.

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REACTIONS OF CYCLIC ESTERS OF PHOSPHOROUS ACID WITH α -HALOKETONES

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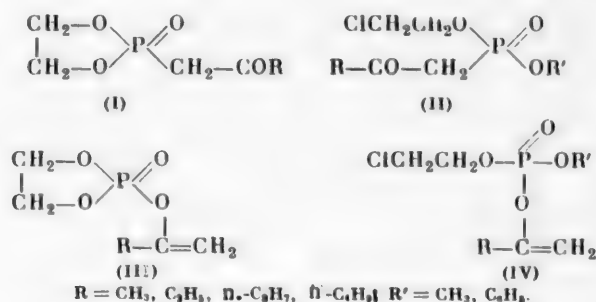
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In previous communications we showed, that reactions of monohalo substituted derivatives of acetone, acetophenone, and other ketones with esters of phosphorous acid simultaneously proceed in two directions: According to the Arbuzov rearrangement with the formation of the corresponding phosphinic acid esters, and according to the "abnormal" scheme with the formation of unsaturated phosphoric acid esters [1-5]. With the di- and polychloro ketone derivatives, and also chloro derivatives of acetoacetic ester, acetylacetone, and phosphonacetone, the reactions take place only in the second direction [6, 7].

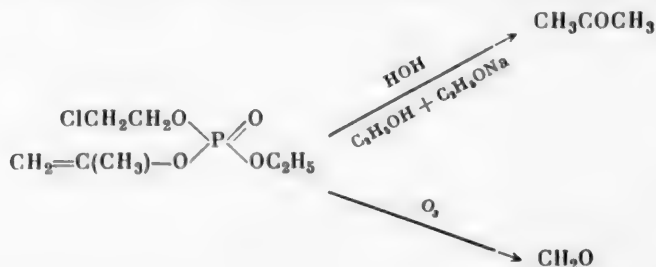
Here we studied the reactions of chloroacetone, chloroacetophenone, and α , α -dichloroacetone with cyclic esters of phosphorous acid: Esters of ethyleneglycol- and methoxypropyleneglycolphosphorous acid.

Theoretically, one can assume these reactions to proceed in four possible directions: According to the Arbuzov rearrangement with the formation of phosphinic acid esters, with preservation or cleavage of the ring, or by the "abnormal" scheme with the formation of phosphoric acid esters, also with preservation or cleavage of the ring. Accordingly, in the case of ethyleneglycolphosphorous acid esters, the formation of products with structures (I-IV) was to be expected.



We studied the reaction of chloroacetone with the methyl, ethyl, propyl, and butyl esters of ethyleneglycolphosphorous acid. In all cases only one product was the result, which contained chlorine in an amount corresponding to formulas (II) and (IV). We did not isolate any alkyl chlorides during the reaction. Consequently, in all cases the reactions take place with cleavage of the ring.

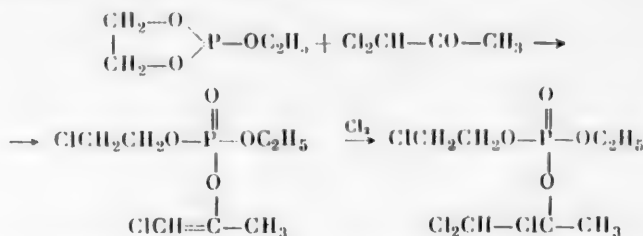
Further investigation of the products obtained showed, that saponification in the presence of sulfuric acid and transesterification with alcohol in the presence of sodium alcoholate, give acetone. Ozonification of one of the pro-



ducts gave a product which was identified as formaldehyde. In their infrared spectra is an absorption band at 1675 cm^{-1} , characteristic of a double bond. From the given data it follows, that the products obtained have the structure (IV), and consequently, the reactions take place according to the "abnormal" type with ring cleavage.

The reaction of the ethyl ester of ethyleneglycolphosphorous acid with chloroacetophenone proceeds analogously.

When the reaction of the ethyl ester of ethyleneglycolphosphorous acid was run with α, α -dichloroacetone, one product was also the result. Its chlorine content corresponded to the formula $\text{C}_6\text{H}_{13}\text{O}_4\text{PCl}_2$. Ethyl chloride was not isolated during the reaction. Earlier we showed, that unsaturated phosphorus esters containing a chlorine atom on a carbon connected to a double bond easily and smoothly add a chlorine molecule [6]. When this reaction was studied, the addition product was prepared in good yield, and it contained four chlorine atoms. It follows, that the reaction between the ethyl ester of ethyleneglycolphosphorous acid and α, α -dichloroacetone also takes place with ring cleavage and the formation of the unsaturated phosphate.



It should be mentioned, however, that the yields of unsaturated phosphates described above are relatively small, ranging from 25 to 50%. A considerable amount of tar is formed; thus it is possible, that to some extent the reactions proceed in some other direction.

The reaction between the ethyl ester of ethyleneglycolphosphorous acid and bromoacetone is more complicated. A small amount of ethyl bromide was detected during the reaction and distillation of the reaction mixture. Consequently, the reaction to some extent takes place with preservation of the ring. At the same time, the main fraction boiling between $128\text{--}130^\circ$ at 10 mm (yield: $\sim 15\%$) contains bromine in an amount close to the one calculated for the formula $\text{C}_7\text{H}_{14}\text{O}_4\text{PBr}$. Ozonization established the presence of a double bond. The reaction evidently proceeds in several directions; the main product is the unsaturated phosphate. The reaction and distillation are accompanied by strong tar formation.

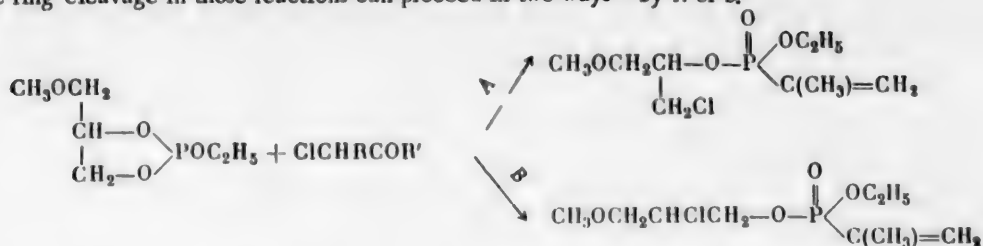
Our results agree with data in [8-11], in which it is shown, that reactions of esters of ethyleneglycolphosphorous acid with alkyl bromides and with chloral as a rule take place with ring cleavage.

Interesting results were obtained when the reaction of haloketones with the ethyl ester of methoxypropyleneglycolphosphorous acid was studied. As was shown earlier, the esters of methoxypropyleneglycolphosphorous acid react very peculiarly with halo derivatives. Thus, the reaction of the ethyl ester with ethyl bromide takes place with preservation of the ring, but the reaction course with acetyl bromide depends on the nature of the ester radical. Methyl and benzyl esters of phosphinic acids which contain rings, but ethyl, propyl, and phenyl esters give those with cleaved rings [12]. The methyl ester of ethoxypropyleneglycolphosphorous acid and chloral give the unsaturated phosphate with preservation of the cyclic structure [11]. As was shown in [13] and in thermographic studies [14], the reactions of cyclic esters of ethyleneglycolphosphorous acid and its derivatives with alkyl bromides proceed in two phases: At lower temperatures the products are predominantly those with cleaved rings, which at higher temperatures give alkyl halides and form cyclic esters of ethyleneglycol alkylphosphinic acids.

Reactions of the ethyl ester of methoxypropyleneglycolphosphorous acid with chloroacetone, α, α -dichloroacetone, and chloroacetophenone could proceed in four different directions with formation of products of type (I-IV), shown above. In the reaction with chloroacetone no formation of ethyl chloride was observed; a product containing the quantity of chlorine and phosphorus sufficient for $\text{C}_9\text{H}_{16}\text{O}_4\text{PCl}$ was obtained. In its infrared spectrum there is an intense absorption band at 1672 cm^{-1} . Transesterification of the product with alcohol in the presence of sodium ethylate gave acetone, identified in the form of its semicarbazone. The data show, that the reaction under consideration proceeds by the "abnormal" scheme and is accompanied by ring cleavage.

Analogous results were obtained by reaction of the ethyl ester of methoxypropyleneglycolphosphorous acid with chloroacetophenone and α, α -dichloroacetone. In both cases ring cleavage took place and unsaturated phosphates were formed.

The ring cleavage in those reactions can proceed in two ways - by A or B:



The final choice between these two directions so far has not been made, but considering possible steric hindrance during the reaction, direction A is more likely.

No cyclic products were noted in the reactions under consideration. As was shown in our previous studies [15], reactions of esters of phosphinic acids with alkyl iodides and bromides to give mixed esters, take place rather easily, but with alkyl chlorides only at elevated temperatures and rather slowly, due to their low reactivity. The cyclization of halo phosphates obtained on reaction of cyclic esters of phosphorous acid with various halo derivatives, is an analogous type of reaction; it should proceed much more easily with bromo esters than with chloro esters. This has been confirmed by results given in [14] and by our work.

EXPERIMENTAL

Reactions of chloroacetone with esters of ethyleneglycolphosphorous acid. 1) Methyl ester. Ester (17 g) and 12.8 g chloroacetone was heated for two hours at 120° under reflux. Formation of methyl chloride during the reaction was not observed. Distillation gave 7.5 g methylisopropenyl-β-chloroethyl phosphate. Much tar was found in the residue from the distillation.

B. p. 126-127.5° at 11 mm, d_4^{20} 1.2470, n_D^{20} 1.4420, MR_D 45.54; calculated 46.29.

Found %: P 14.95; Cl 16.10. $C_6H_{12}O_4PCl$. Calculated %: P 14.43; Cl 16.55.

2) Ethyl ester. To 50 g. ester was added 34 g chloroacetone. The temperature of the reaction mixture rose to 50°. It was heated for five more hours at 120-130°. Ethyl chloride was not found. Distillation gave 34.3 g ethylisopropenyl-β-chloroethyl phosphate.

B. p. 134-136° at 11 mm, d_4^{20} 1.1990, n_D^{20} 1.4430, MR_D 50.84; calculated 50.91.

Found %: P 13.75; Cl 15.35. $C_7H_{14}O_4PCl$. Calculated %: P 13.55; Cl 15.54.

Specific products could not be isolated by distillation of higher boiling fractions (140-159° at 12 mm, 7.8 g).

Saponification. The phosphate (4 g) was heated with 8 ml 30% sulfuric acid on a steam bath in a flask connected with a downward condenser. About 0.6 g acetone was distilled off, b.p.: 56-57°; semicarbazone m.p.: 187°.

Transesterification. To an alcoholic solution of sodium ethylate prepared from 0.1 g sodium and 8 ml anhydrous alcohol, was added 5 g phosphate. The reaction mixture was heated on a boiling water bath in a flask connected with a downward condenser. The distillate of alcohol with acetone was used for the preparation of the semicarbazone. Semicarbazone melted at 188°. Mixed melting point test, m.p.: 187°.

Ozonization. To a solution of 2.5 g phosphate in 20 ml anhydrous carbon tetrachloride was added over a period of 18 hours ozonized oxygen. The ozonide decomposed on heating with water, the distillate was collected in a solution of dimedon. The condensation product melted at 188°. Mixed melting point test with the formaldehyde derivative gave m.p.: 188°.

3) Propyl ester. The reaction was conducted with 50 g propyl ester and 33 g chloroacetone over a period of four hours at 150°. This gave 31.2 g propylisopropenyl-β-chloroethyl phosphate. The infrared spectrum showed an intense absorption band at 1675 cm^{-1} .

B. p. 137-138° at 10 mm, d_4^{20} 1.1619, n_D^{20} 1.4438, MR_D 55.45; calculated 55.53.

Found %: P 12.67; Cl 14.32. $C_8H_{16}O_4PCl$. Calculated %: P 12.78; Cl 14.64.

No specific product was isolated on distillation of the fraction boiling at 145-160°, obtained in the amount of 5.6 g.

Transesterification. The alcoholic solution of sodium ethylate was heated with 5 g of the ester on a boiling water bath. The distillate gave a semicarbazone with m.p. 187.5°. Mixed melting point test with the acetone derivative gave m.p.: 188°.

4) **Butyl ester.** The reaction was conducted with 36.8 g ester and 20.8 g chloroacetone. This gave 30.2 g butylisopropenyl- β -chloroethyl phosphate.

B. p. 148-150° at 10 mm, d_4^{20} 1.1390, n_D^{20} 1.4432, M_{rD} 59.78; calculated 60.15.
Found %: P 12.10; Cl 13.65. $C_9H_{18}O_4P$. Calculated %: P 12.09; Cl 13.84.

Saponification. The phosphate (5 g) was heated with 10 ml 30 % sulfuric acid. Semicarbazone m.p.: 187°. Mixed melting point test with the acetone semicarbazone gave 187°.

Reaction of the ethyl ester of ethyleneglycolphosphorous acid with α , α -dichloroacetone. 22 g α , α -dichloroacetone was added dropwise to 23.6 g ester. A temperature rise of the reaction mixture to 50° occurred. The reaction mixture was heated 1.5 hours at 140-150°. Formation of ethyl chloride was not observed. Distillation yielded 7.8 g of a fraction boiling to 120° at 10 mm, and 20 g boiling in the 128-148° range at 10 mm. Distillation of the second fraction yielded 12.2 g of the ethyl ester of chloroisopropenyl- β -chloroethylphosphoric acid.

B. p. 149.5-150.5° at 10 mm, d_4^{20} 1.2915, n_D^{20} 1.4570, M_{rD} 55.47; calculated 55.79.
Found %: P 11.52; Cl 27.10. $C_6H_{13}O_4PCl_2$. Calculated %: P 11.80; Cl 26.96.

Chlorination. Through a solution of 9 g ethyl chloroisopropenyl- β -chloroethyl phosphate in 20 ml dry carbon tetrachloride was passed, under cooling with ice water and slowly, a stream of chlorine until a weight gain of 1.4 g. Distillation gave 4.1 g ethyl- β -chloroethyl(α -chloro- β , β -dichloroisopropyl) phosphate.

B. p. 171-173° at 7 mm, d_4^{20} 1.4290, n_D^{20} 1.4750, M_{rD} 65.67; calculated 65.77.
Found %: P 9.18; Cl 43.00. $C_7H_{13}O_4PCl$. Calculated %: P 9.30; Cl 42.50.

Reaction of the ethyl ester of ethyleneglycolphosphorous acid with chloroacetophenone. Ester (20 g) and 18 g chloroacetophenone was heated for 9 hours at 150°. Ethyl chloride did not form. Distillation gave 14.1 g ethyl α -phenylethenyl- β -chloroethyl phosphate. Much tar formed during the reaction and distillation.

B. p. 164-165° at 2 mm, d_4^{20} 1.2348, n_D^{20} 1.5105, M_{rD} 70.39; calculated 70.41.
Found %: P 10.83; Cl 11.99. $C_{12}H_{16}O_4PCl$. Calculated %: P 10.67; Cl 12.2.

Reaction of the ethyl ester of methoxypropyleneglycolphosphorous acid with α -haloketones. 1) **Chloroacetone.** Ester (25 g) and 21.8 g chloroacetone was heated five hours at 120-130°. Ethyl chloride did not form. Repeated distillation of the reaction mixture yielded 16.2 g ethyl methoxychloroisopropylisopropenyl phosphate. The infrared spectrum, taken on an IKS-14 apparatus, showed an intense absorption band at 1672 cm^{-1} .

B. p. 155-156° at 12 mm, d_4^{20} 1.1787, n_D^{20} 1.4440, M_{rD} 61.34; calculated 61.45.
Found %: P 11.15; Cl 13.31. $C_9H_{18}O_4PCl$. Calculated %: P 11.37; Cl 13.02.

Transesterification. To a solution of sodium alcoholate prepared from 0.1 g sodium and 8 ml absolute alcohol was added 5 g ethyl methoxychloroisopropylisopropenyl phosphate. The mixture was heated in a flask with a reflux condenser on a boiling water bath. The distillate obtained was used for the preparation of the semicarbazone, m.p.: 186°. A mixed melting point test with the acetone derivative gave m.p.: 187°.

2) **Chloroacetophenone.** A mixture of 27 g ester and 23.7 g chloroacetophenone was heated for nine hours at 150°. Formation of ethyl chloride was not noted. Distillation yielded 13.1 g ethyl methoxychloroisopropyl- α -phenylethenyl phosphate.

B. p. 184-185° at 10 mm, d_4^{20} 1.2168, n_D^{20} 1.5080, M_{rD} 81.04; calculated 81.28.
Found %: P 8.88; Cl 10.39. $C_{14}H_{20}O_5PCl$. Calculated %: P 9.25; Cl 10.06.

3) **α , α -Dichloroacetone.** The reaction was conducted with 21 g ester and 15.3 g dichloroacetone. At first the reaction went slowly, but on heating to 100° the reaction mixture spontaneously heated up to 160°. The solution turned dark. Distillation gave 12.8 g ethyl methoxychloroisopropylchloroisopropenyl phosphate.

B. p. 170-172° at 10 mm, d_4^{20} 1.2513, n_D^{20} 1.4548, M_{rD} 66.54; calculated 66.66.
Found %: P 10.37; Cl 23.00. $C_9H_{17}O_5PCl_2$. Calculated %: P 10.09; Cl 23.10.

SUMMARY

Reaction of esters of ethyleneglycolphosphorous acid and ethyl ester of methoxypropyleneglycolphosphorous acid with chloroacetone, chloroacetophenone, and α , α -dichloroacetone takes place with ring cleavage and the formation of unsaturated phosphates.

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NEW SYNTHETIC METHOD FOR ESTERS
OF PHOSPHINIC AND THIOPHOSPHINIC ACIDS
XXXVIII. SYNTHESIS OF ESTERS OF UNSATURATED PHOSPHINIC
AND THIOPHOSPHINIC ACIDS

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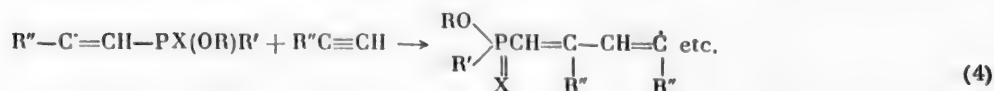
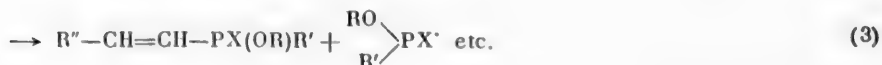
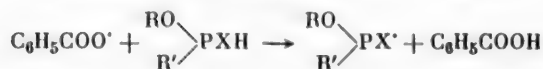
Original article submitted July 25, 1960

At the present, researchers give much attention to esters of unsaturated phosphinic and thiophosphinic acids. The following reactions are being studied: Addition of various nucleophilic reagents [1-4], diene synthesis [2, 5], polymerization and copolymerization [6-8]. By the last reactions various polymers containing phosphorus in the side chain, with lowered combustibility have been obtained. Various methods were used to prepare esters of unsaturated phosphinic and thiophosphinic acids: Arbuzov and Michaelis-Bekker, based on halo allyl addition of phosphorous acid esters [9] and salts of dialkylphosphorous acids [10], splitting off of hydrogen halide, bromine or water from the respective ester derivatives of phosphinic acids, action of alcohols, mercaptans, and their sodium derivatives on acid chlorides of unsaturated phosphorus acids [11].

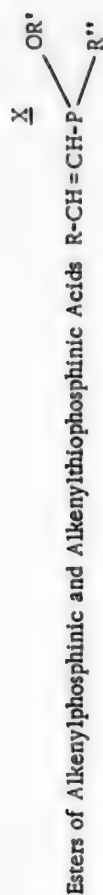
One of these authors found earlier, that various derivatives of unsaturated phosphates can be prepared by addition of partial esters of phosphorus acids to acetylenic compounds, activated by some electron withdrawing group. The reactions take place in the presence of an alkaline catalyst [12]. In this work we proved, that this synthetic method can be expanded directly to acetylenic hydrocarbons, provided the reaction is conducted under conditions which stimulate the addition via a radical mechanism.

The following partial esters of phosphorus acid were used by us: Dimethyl and diethyl esters of phosphorous acid, diethyl and diisopropyl esters of thiophosphorous acid, ethyl and isopropyl esters of ethylphosphinous acid.

Additions to heptyne-1 and octyne-1 in the presence of benzoyl peroxide or by exposure of the reaction mixture to ultraviolet light were successful. The reaction course can be represented by the following equations:



X = O, S; R = CH₃, C₂H₅, iso-C₃H₇; R'' = C₆H₁₁, C₆H₁₃; R' = C₂H₅O, C₂H₅, CH₃O, iso-C₃H₇.



No.	Values				Yield (%)	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	M.R.		Phosphorus content (in %)		Double bond content (%)
	R	R'	R''	X					Found	Calculated	Found	Calculated	
1	C ₅ H ₁₁	CH ₃	CH ₃ O	O	20	154—155° (20)	1.4725	1.0612	54.39	54.16	15.03	15.04	87
2	C ₃ H ₁₁	C ₂ H ₅	C ₂ H ₅ O	O	28	149—150 (12)	1.4630	1.0201	63.22	63.39	13.47	13.24	89
3	C ₆ H ₁₃	C ₂ H ₅	C ₂ H ₅ O	O	44	151—152 (9)	1.4688	1.0122	68.14	68.01	12.55	12.50	93
4	C ₅ H ₁₁	C ₂ H ₅	C ₂ H ₅ O	S	45	119 (1)	1.4800	0.9972	71.19	70.88	12.39	12.40	87
5	C ₃ H ₁₁	iso-C ₃ H ₇	iso-C ₃ H ₇	S	44	144—145 (13)	1.4720	0.9730	80.02	80.11	10.80	11.15	90
6	C ₆ H ₁₃	C ₂ H ₅	C ₂ H ₅ O	S	57	149—150 (9)	1.4795	0.9933	75.37	75.49	11.39	11.72	89
7	C ₃ H ₅	C ₂ H ₅	C ₂ H ₅ O	S	40	146 (3)	1.5450	1.1190	72.31	71.90	12.18	12.11	87
8	C ₃ H ₁₁	C ₂ H ₅	C ₂ H ₅	O	27	124—125 (3)	1.4560	0.9572	61.91	62.26	14.41	14.20	93
9	C ₃ H ₁₁	iso-C ₃ H ₇	C ₂ H ₅	O	27	145—147 (12)	1.4530	0.9423	66.59	66.87	13.29	13.36	93
10	C ₆ H ₁₃	C ₂ H ₅	C ₂ H ₅	O	31	157—158 (15.5)	1.4585	0.9568	66.18	66.87	13.15	13.36	94

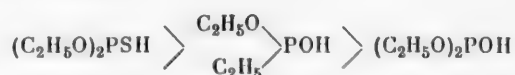
Reactions (1), (1a), (2) and (3) require initiation, chain increase, and formation of an addition product, (4) – the formation of polymeric radical at the expense of further telomerization. The reactions were conducted with equimolar quantities of reagents, at 80–95°, 30–130 hours, under constant exposure to a mercury-quartz lamp, or heating with a small quantity of benzoyl peroxide. In both cases the same esters of alkenylphosphinic and alkenylthiophosphinic acid were obtained in 25–50% yield. The esters are colorless, highly mobile liquids, almost insoluble in water, readily soluble in organic solvents. Their characteristics are given in the Table.

The structure of the addition products was proved by using the diethyl ester of heptenylthiophosphinic acid as an example. *n*-Caproic acid was obtained after its oxidation with potassium permanganate.

The infrared spectrum of the compound has an intense absorption band at 1616 cm^{-1} which is characteristic of valence vibrations of the double bond $\text{C}=\text{C}$. Some shift of the absorption band toward the lower frequencies can be explained by conjugation of the carbon-carbon double bond and the $\text{P}=\text{S}$ -group.

From these results we deduced, that the addition of partial esters of phosphorus acids to acetylenic hydrocarbons, initiated by benzoyl peroxide or light, goes against the Markovnikov rule. The results agree with data of other authors concerning the addition to acetylenic hydrocarbons of hydrocyanic acid, alcohols, thioacetic acid, and other reagents [13, 14].

The reactivities of a number of phosphorus acid esters were compared in regard to addition reactions to alkynes. We compared the addition rate to heptyne-1 of acid ethyl esters of phosphorous, thiophosphorous, and ethylphosphinous acids under ultraviolet irradiation. The reaction rate was characterized by change in the acid concentration in the reaction mixture. As can be seen on Figure 1, the acid esters can be arranged in the following order according to decrease in reactivity in that type of reaction:



Using diethylphosphorous acid as an example, we made comparative studies on the addition of partial esters of phosphorus acids to ethylenic and acetylenic hydrocarbons: Heptene-1, pentyne-1, and phenylacetylene. Reactions also took place under ultraviolet irradiation. It follows from Figure 2, that the reactivity of hydrocarbons in that type of reaction decreases in the order:

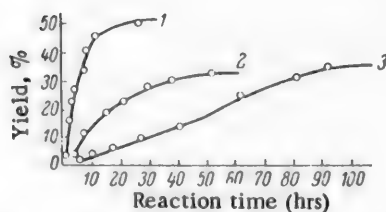


Fig. 1. Reaction rates of heptyne-1 with acid esters of phosphorus acids under ultraviolet irradiation. 1) diethylthiophosphorous acid; 2) acid ethyl ester of ethylphosphinous acid; 3) diethylphosphorous acid.

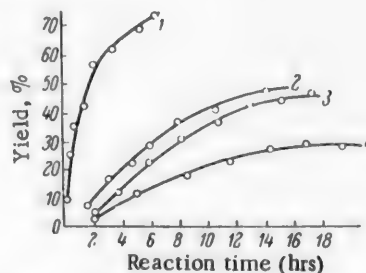


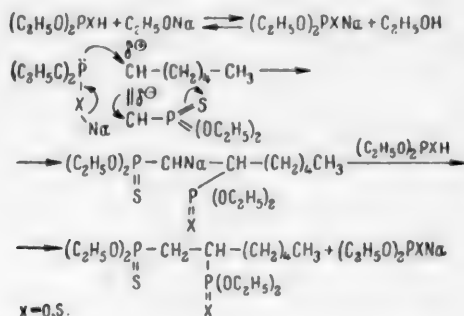
Fig. 2. Reaction rates of diethylthiophosphorous acid with unsaturated hydrocarbons under ultraviolet irradiation. 1) Heptene-1; 2) heptyne-1; 3) heptyne-1 in the presence of benzoyl peroxide; 4) phenylacetylene.

Using diethylphosphorous acid and heptyne-1 as an example, it was proved that the addition rate under the conditions used by us was approximately the same under ultraviolet irradiation and heating with benzoyl peroxide.

We also studied the addition reactions of a number of partial esters of phosphorus acids to phenylacetylene. These reactions, under irradiation and with benzoyl peroxide, are less active than addition reactions to heptyne-1 and octyne-1, and are accompanied by much tar formation in the reaction mixture. Because of this, the yields of

addition products are very low. The addition product of diethylthiophosphorous acid to phenylacetylene, i.e., diethyl ester of β -phenylvinylthiophosphinic acid, was prepared in pure form and was characterized. The compound has been described in the literature [15], but the given constants (b.p. 130° at 1 mm, n_D^{20} 1.5658, d_4^{20} 1.1067) differ from those determined by us (see Table, No. 7). The molecular refraction expected on the basis of these constants is considerably different from the calculated one. Apparently the compound was not sufficiently pure.

Some of the esters of unsaturated phosphinic and thiophosphinic acids obtained by us we used for the preparation of diphosphinic derivatives by adding to them partial esters of phosphorus acids. It seems to us that such compounds could be of great interest as plasticizers for various materials. Diethylphosphorous and diethylthiophosphorous acids were successfully added to the diethyl ester of heptenylthiophosphinic acid. The addition takes place in the presence of sodium ethylate under heating for several hours to 100-120°. The reaction proceeds by an ionic mechanism, according to the scheme:



The addition products - 1, 2-di(diethylphosphonothio)- and 1, 2-diethylthiophosphonodiethylphosphonoheptanes - are thick, colorless liquids, hardly soluble in water, soluble in organic solvents.

EXPERIMENTAL

Heptyne-1 and octyne-1 were prepared by the splitting off of hydrogen bromide from 1, 2-dibromoheptane and 1, 2-dibromooctane [16], and phenylacetylene by the splitting off of hydrogen bromide from monobromostyrene [17].

Addition reactions. a) An equimolar mixture of the partial ester of phosphorous, thiophosphorous, or phosphinous acid and alkyne was mixed in a quartz flask, and irradiated continuously with a mercury quartz PRK-2 lamp at a distance of 5-6 cm, for 30-130 hours, at 90-95°.

b) An equimolar mixture of reagents was heated under reflux on a glycerin bath in the presence of benzoyl peroxide for 30-130 hours at 80-85°. The benzoyl peroxide was added several times during the reaction in portions representing 1% of the reagents' weight. The addition products were isolated by vacuum distillation.

Oxidation of the diethyl ester of heptenylthiophosphinic acid. The diethyl ester of heptenylthiophosphinic acid (11.5 g) dissolved in 1000 ml water was oxidized with 23.7 g powdered potassium permanganate at a temperature no higher than 10°. The potassium permanganate was added periodically to the reaction mixture in small portions. The following day the precipitate of manganese dioxide was filtered, treated with hot water, the filtrate evaporated, acidified with dilute sulfuric acid, and several times extracted with ether. The ether extract was dried over sodium sulfate. After distillation of the ether, the residue was vacuum distilled. This gave 2.5 g n-caproic acid, which after two distillations had the following constants:

B. p. 110-112° (26 mm), n_D^{20} 1.4165, d_4^{20} 0.9283, MR_D 31.37; calculated 31.56.
Literature data: B. p. 205°, n_D^{20} 1.4164, d_4^{20} 0.929 [18].

Addition of diethylphosphorous acid to the diethyl ester of heptenylthiophosphinic acid. To the reaction mixture consisting of 8 g diethyl ester of heptenylthiophosphinic acid and 4.4 g diethylphosphorous acid was added, dropwise, a saturated alcoholic solution of sodium ethylate. The temperature of the reaction mixture rose by 10°. Then the mixture was heated on a glycerin bath at 120-125° for 10 hours. After two distillations the yield was 3 g of 1-diethylphosphono-2-diethylthiophosphono-heptane:

B. p. 169-170° (2 mm), n_D^{20} 1.4640, d_4^{20} 1.0810, MR_D 101.6; calculated 101.73.
Found %: P 15.63. $C_{15}H_{34}O_5P_2$. Calculated %: P 15.59.

Addition of diethylthiophosphorous acid to the diethyl ester of heptenylthiophosphinic acid. The reaction was conducted analogously to the one described above, with 45 g diethylthiophosphorous acid and 8 g diethyl ester of heptenylthiophosphinic acid in the presence of sodium ethylate. Distillation of the reaction mixture gave 7 g of 1, 2-di(diethylthiophosphono)heptane:

B. p. 206-207° (8 mm), n_D^{20} 1.4854, d_4^{20} 1.0765, MR_D 107.60; calculated 107.16.

Found %: P 15.31. $C_{15}H_{34}O_4P_2S_2$. Calculated %: P 15.34.

SUMMARY

1. It was demonstrated, that partial esters of phosphorous, thiophosphorous, and ethylphosphinous acid add to acetylenic hydrocarbons in the presence of benzoyl peroxide or under irradiation of the reaction mixture with ultra-violet light. The addition products – esters of ethylalkenyl – and alkenylphosphinic and – thiophosphinic acids – were obtained in 25-50% yields.

2. The addition of partial esters of phosphorus acids to acetylenic hydrocarbons proceeds by a chain radical mechanism, against the Markovnikov rule.

3. It was demonstrated, that diethyl- and diethylthiophosphorous acids add to the diethyl ester of heptenylthiophosphinic acid in the presence of sodium ethylate.

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STUDIES IN THE NAPHTHALENE SERIES

XXI. THE ACTION OF AMMONIA ON NAPHTHOLATES

AND SOME NAPHTHOL ETHERS*

V. V. Kozlov and I. K. Vesclovskaya

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Original article submitted March 28, 1960

The role of the keto form of naphthols is notable in many conversions, specially in amination [1], alkylation [2], halogenation [3], and other reactions. When we studied the kinetics of amination of α - and β -naphthols, we also demonstrated the significance of their tautomeric forms [4]. There are indications, that under the effect of soda the absorption spectrum of β -naphthol in solution shifts, due to a upset of the tautomeric equilibrium [5]. It is known, that substitution of a hydrogen in the hydroxyl group of naphthols by sodium changes their reactivity: While the hydrogenation of α - and β -naphthols leads to a mixture of aliphatic and aromatic tetrahydronaphthols, with predominance of the former, hydrogenation in the presence of sodium alcoholate leads to the predominant formation of aromatic compounds [6]. It is quite possible that the latter are obtained as a result of hydrogenation of a naphthol which is preeminently in the enol form under the effect of the alcoholate.

TABLE 1. Amination of α - and β -naphthols and their naphtholates by ammonia and ammonia with ammonium sulfite (0.1 gram-mole naphthol or naphtholate, 100 ml 25% ammonia, 3 hrs; 0.04 gram-mole ammonium sulfite, 0.54 gram-mole ammonia, to 50 ml water)

Charge	Naphthol residue (in %)	Naphthylamine obtained (in %)
With ammonia at 250°		
β -Naphthol	32.2	58.0
β -Sodium naphtholate	78.5	11.0
Same with 0.1 gram-mole NaOH	88.9	14.1
Same with 0.5 gram-mole NaOH	95.5	4.6
Barium β -naphtholate	49.0	42.3
Same with 0.25 gram-mole Ba(OH) ₂	53.0	24.8
α -Naphthol	67.0	23.2
Sodium α -naphtholate	90.5	2.8
With ammonia and ammonium sulfite at 180°		
β -Naphthol	14.3	81.8
Sodium β -naphtholate	90.6	10.6
With ammonia and sodium sulfite at 180°		
β -Naphthol	56.4	40.3
Sodium β -naphtholate	93.5	0.85

*Communication XX, see *ZhOKh*, 30, 4088 (1960).

We studied the behavior of ammonia, at 180–250° in an autoclave, toward such derivatives of α - and β -naphthols which respond to the "fixed" enol form, such as sodium and barium naphtholates, some simple and mixed esters of naphthols and naphthoxyacetic acids. Direct amination of these compounds can be expected, since in all the conversions there is no significant activity decrease for naphthol ethers [7].

Table 1 gives results of heating sodium and barium naphtholates with ammonia.

From these data it follows, that both naphthols in their naphtholate forms are aminated with great difficulty. A much smaller quantity of naphthylamine is formed when naphtholates are heated with ammonia in the presence of an excess of caustic. A similar picture exists when β -naphthol and sodium β -naphtholate are heated with ammonia in the presence of ammonium or sodium sulfite (Table 1). Under those conditions the "fixed" enol form again does not promote the addition of a bisulfite molecule, and consequently the formation of β -naphthylamine. The sharply lowered yield of β -naphthylamine when β -naphthol and β -naphtholate is aminated in the presence of sodium sulfite, as compared to the yields in the case of ammonium sulfite (Table 1), was explained by us before [4] by the lowered ability of sodium sulfite to hydrolyze and thus form bisulfite necessary for the reaction, as compared to the hydrolysis of ammonium sulfite. On the other hand, even partial hydrolysis of sodium nitrite leads to a more alkaline medium, which in turn lowers the hydrolysis of naphtholate, and the result is a lower yield of naphthylamine. The great stability of α -naphtholate during the amination of naphtholates confirms the lower reactivity of α -naphthol, as we observed it when studying the kinetics of amination of that compound [4]. Heating of methyl ethers of naphthols with 25% ammonia at 250° gave a mixture containing considerable quantities of unchanged substance, naphthol, as well as the product of dealkylation and of naphthylamine as the product of its amination. The methyl ether of β -naphthol is more stable than is the ether of α -naphthol (Table 2).

Small quantities of β -naphthylamine formed only after six hours of heating of the methyl ether of β -naphthol with an equivalent amount of caustic soda. This shows, that under sufficiently strenuous conditions, such as pressure, action of aqueous solutions of hydroxides of alkaline and alkaline earth metals, it is possible to split off alkyls in many

TABLE 2. Heating of ethers of α - and β -naphthols with ammonia and with ammonia and ammonium sulfite (0.05 gram-mole ether, 50 ml 25% ammonia, 250°; 0.02 gram-mole ammonium sulfite, 37 ml 25% ammonia, to 50 ml water, 180°)

Charge	Time (in hrs)	Obtained (in %)		
		initial substance	naphthol	naphthyl- amine
With ammonia at 250°				
Methyl ether of β -naphthol	{ 1	61.7	21.3	8.1
	2	39.5	29.6	15.3
	3	38.2	16.5	27.5
Same with 0.06 gram-mole NaOH	{ 3	15.9	77.4	—
	6	0.4	87.4	7.4
Methyl ether of α -naphthol *	{ 3	21.8	61.4	16.6
	3	96.5	Traces	—
Propyl ether of β -naphthol	3	95.8	—	—
Isoamyl ether of α -naphthol	3	99.5	—	—
Acetate of β -naphthol	{ 1	—	19.5	61.2
	3	—	9.4	78.3
β -Naphthoxyacetic acid	3	95.6	—	—
α -Naphthoxyacetic acid	3	50.3	18.7	24.5
With ammonia and with ammonium sulfite at 180°				
Propyl ether of β -naphthol	3	99.8	—	—
Isoamyl ether of α -naphthol	3	97.8	—	—
Acetate of α -naphthol	3	10.5	3.0	82.5
β -Naphthoxyacetic acid	3	96.3	—	—
α -Naphthoxyacetic acid	1	100.0	—	—

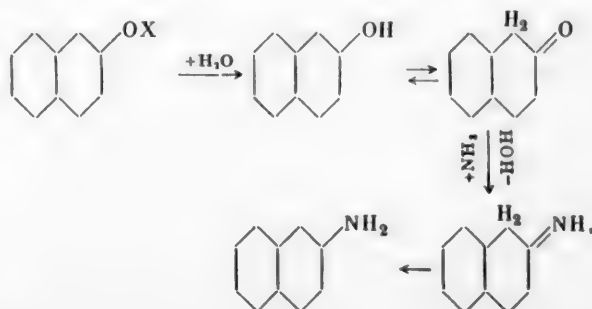
alkyl hydroxy compounds [8]. In addition, these experiments also confirm, as we showed above, that β -naphtholate which forms as a product of dealkylation of the ether by caustic cannot be aminated. When the propyl ether of β -naphthol and isoamyl ether of α -naphthol is heated in an autoclave with ammonia, at 250°, and with ammonia in the presence of ammonium sulfite at 180°, the compounds do not change and no conversion products are obtained (Table 2). Thus, various alkoxy derivatives of naphthols are stable when heated with concentrated ammonia at high temperatures and pressure, and only methoxynaphthols dealkylate at 250° to an extent of 60% for β -naphthol and 80% for α -naphthol. The heating of β -naphthoxyacetic acid with ammonia and ammonium sulfite at 180°, and of α -naphthoxyacetic acid at 250° did not convert the compounds. However, when α -naphthoxyacetic acid was heated with ammonia at 250°, in contrast with its isomer it split to an extent of 50% and α -naphthol as well as α -naphthylamines were found in the reaction mixture (Table 2). Naphthoxyacetic acids are sufficiently stable under the action of aqueous solutions of caustic. Thus, for instance, α -naphthoxyacetic acid heated in an autoclave at 250° for three hours with 1N NaOH was converted only 40-45% to α -naphthol. Heating of the acetate of β -naphthol with ammonia after only one hour resulted in the disappearance of ester and a considerable yield of β -naphthylamine. The latter is not a conversion product of the ester proper, but a product of the amination of β -naphthol formed on hydrolysis of the ester. Such a hydrolysis of the β -naphthol acetate goes 84% on mere heating with ammonia for 50 min under reflux.

TABLE 3. Heating of the K salt of the acid sulfate of β -naphthol with ammonia (0.025 gram-mole 97.5% ester; 50 ml 25% ammonia)

Temperature	Time (in hours)	Obtained (in%) *	
		β -Naphthylamine	Unchanged ester
200°	3	—	100.0
225	3	5.7	88.7
237	3	32.2	58.4
250	1	23.0	65.3
250	2	76.5	18.2
250	3	82.6	4.0

The conversion of the K salt of the acid sulfate of β -naphthol goes rather smoothly on heating with ammonia in an autoclave, and large quantities of β -naphthylamine are formed (Table 3). The formation of the latter, however, is not the result of amination of the ester proper either, but takes place at the expense of β -naphthol formed during hydrolysis. No β -naphthylamine formed when the K salt of the acid sulfate of β -naphthol was heated with ammonia in the presence of an equimolar amount of sodium hydroxide for three hours at 250°. In that case a considerable quantity of ester remained (82.6%), and β -naphthol was formed (11.2%). The ester is not stable when heated with water in an autoclave. Its conversion to β -naphthol starts at rather low temperatures (50% at 200°), and reaches quantitative yield at 250° after three hours. The same result was obtained when the ester was heated at 250° for three hours in a 2.5% solution of sodium acetate, which produces a hydrogen ion concentration of $1.6 \cdot 10^{-9}$, corresponding to a hydrogen ion concentration of a 25% ammonia solution. When we take into account the partial tarring of the ester which occurs during its heating with ammonia, then the quantity of β -naphthylamine formed equals that of β -naphthol during the hydrolysis of the ester with water.

On the basis of these accounts, the conversions of naphthols can be expressed by the following basic scheme (on β -derivatives as example):



The side products are: Di(naphthylamines), di(naphthols), and other products of oxidizing condensations.

EXPERIMENTAL

1. Experiments on heating with ammonia were conducted in a rotary steel autoclave of 200 ml capacity, without agitator. The rise to the required temperature was accomplished in 30 minutes. During amination of α -naphthol (m.p. 94°) and β -naphthol (m.p. 122°) and their naphtholates, the contents of the autoclave were treated with a 5% solution of caustic soda. The residue on the filter was washed until all naphthol had been removed with a caustic solution, then with water, dried, and weighed. A part of the precipitate was dissolved in 5% hydrochloric acid and filtered from the insoluble portion, which consisted of di(α - and β -naphthylamine), and tar. The content of α - or β -naphthylamine was determined by titration of the acid filtrate with 0.1 N solution of sodium nitrite. The washings were combined with the main caustic solution and the naphthol content determined by coupling with 0.05 N solution of diazo-*p*-nitrobenzene in bicarbonate medium. The rest, which did not dissolve in dilute alkalies and acid, was crystallized from benzene, and gave: di(α -naphthylamine) melting at 109-111.0° and, respectively, di(β -naphthylamine) melting at 168-170°.

2. Sodium naphtholates were prepared by solution of naphthol in a calculated quantity of caustic soda, and put into the autoclave in solution. The barium naphtholate was prepared by mixing an aqueous suspension of barium hydroxide and naphthol, followed by drying at 90-100°.

3. The methyl ether of β -naphthol was used in its commercial form, with m.p.: 72°. When heated with ammonia, β -naphthol and β -naphthylamine were formed, as shown above, and steam distillation of the residue insoluble in alkalies and acid gave unchanged methyl ether. When the methyl ether of α -naphthol [9] (b.p. 265°) was heated with ammonia, the initial product was obtained in the form of an oil on the bottom of the autoclave; it was isolated, dissolved in ether, washed with weak hydrochloric acid, water, and the solvent evaporated. Extraction with ether first yielded α -naphthylamine from the ammonia solution, and then after neutralization ether extraction also yielded α -naphthol.

4. The isoamyl ether of α -naphthol was prepared by heating isoamyl alcohol with α -naphthol in the presence of sulfuric acid (b.p. 178°). After heating with ammonia the ether remained on the bottom of the autoclave in the form of an oil. It was extracted with ether, washed with a weak solution of caustic soda, water, and the solvent evaporated.

5. The propyl ether of β -naphthol [10] (m.p. 40°) was heated with ammonia and found practically unchanged in the precipitate.

6. Acetate of β -naphthol [11] (m.p. 70°) was heated with ammonia and ammonium sulfite and found in the precipitate with β -naphthylamine. The latter was separated by dilution in weak hydrochloric acid.

7. β -Naphthoxyacetic acid [12] (m.p. 156°) was heated with ammonia and was found almost completely in the precipitate. Only an insignificant amount of it was recovered by acidification of the filtrate. α -Naphthoxyacetic acid [13] (m.p. 192°) was heated with ammonia and was found in the solution mixed with a dark oil. The ammoniacal solution was neutralized with hydrochloric acid to a strong acidic reaction and filtered from the naphthoxyacetic acid formed. The dark oil was treated with ether. Part of the extract was washed with a weak caustic soda solution. The alkaline extract was acidified and yielded α -naphthol. The other part of the ether extract was treated with hydrochloric acid, and it yielded α -naphthylamine as the hydrochloride.

8. The reaction mass from heating the K salt of the acid sulfate of β -naphthol [14] with ammonia was filtered from the precipitate containing naphthylamine and tar. The solution was heated with concentrated hydrochloric acid in a flask with a reflux condenser for 45 minutes. Hydrolysis of the ester gave β -naphthol, which was determined as above.

SUMMARY

1. The following were heated with ammonia and ammonia in the presence of ammonium sulfite: α - and β -Naphtholates, methyl ethers of α - and β -naphthols, acetates and acid sulfates of β -naphthols. Hydrolysis of these compounds to naphthols lead to the amination of the latter to naphthylamines.

2. The isoamyl ether of α -naphthol, propyl ether of β -naphthol, and β -naphthoxyacetic acid were completely unchanged on heating with ammonia, and formed no naphthylamines. α -Naphthoxyacetic acid is less stable, and is converted to naphthol to an extent of 50%, and then to α -naphthylamine.

3. Naphthol derivatives which cannot react in the keto form or give addition products corresponding to it, cannot be aminated by ammonia.

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FREE RADICAL REACTIONS OF BIS(CYCLOPENTADIENYL) DIPHENYLTITANIUM

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True organotitanium compounds, with the Ti-C bond, have been known only in the last decade. The first representative was synthesized in 1952, namely phenyltriisopropoxytitanium [1]. Recently the synthesis of alkyl derivatives of the type $R_n TiCl_{4-n}$, where $R = CH_3, C_2H_5, C_4H_9$ [2, 3], was reported. At present a complete organotitanium compound, namely tetramethyltitanium [4], has been prepared. All the mentioned compounds are thermally unstable, and can be maintained only at temperatures in the -70 to -80° range.

Cyclopentadienyl derivatives of titanium are more stable, since they have a structure similar to that of ferrocene. The known π -dicyclopentadienyl derivatives of 2, 3, 4-valent titanium have very different properties. Thus, neutral bis(cyclopentadienyl) titanium [5] can exist only in the absence of oxygen at ordinary temperatures, while the dihalo derivatives of bis(cyclopentadienyl) titanium do not react with oxygen at all [6]. They are interesting, because with aluminum alkyls or aryls they form soluble complexes which catalyze the polymerization of α -olefins [7]. The atoms of the halide in $(C_5H_5)_2TiX_2$ are mobile [8], which makes it possible to substitute them by alkyl or aryl radicals. Thus, when $(C_5H_5)_2TiCl_2$ reacts with methyl-magnesium chloride or dimethylaluminum chloride, the products are $(C_5H_5)_2Ti(CH_3)Cl$ [9] and $(C_5H_5)_2Ti(CH_3)_2$ [10].

Derivatives of $(C_5H_5)_2TiAr_2$ ($Ar = \text{phenyl, m- or p-tolyl, p-dimethylaminophenyl}$), prepared by reaction of $ArLi$ with $(C_5H_5)_2TiCl_2$ in ether solution, are described in [11, 12]. The thermal stability of the yellow crystalline substances obtained changes with the nature of the aryl group. Diphenyl-, m- and p-ditolyl derivatives can be kept at room temperature for several days, while di-p-dimethylaminophenylbis(cyclopentadienyl) titanium completely decomposes at $25-30^\circ$ within several hours. Thermal decomposition of these compounds at 105° in a nitrogen atmosphere gave the corresponding ArH and other unexplained products. In addition, it is known that $(C_5H_5)_2Ti(C_6H_5)_2$ in ether solution and with an excess of phenyllithium gives the dark complexes $(C_5H_5)_2Ti(C_6H_5)_3Li$ or $(C_5H_5)_2Ti(C_6H_5)_4Li_2$; hydrolysis of the latter regenerates the original diaryl derivative. This exhausts the information on the chemical properties of this class of compounds.

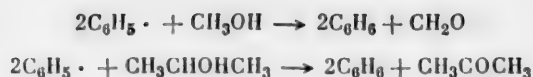
We thought it interesting to make a detailed study on the behavior of $(C_5H_5)_2Ti(C_6H_5)_2$ under reaction conditions which previously led to phenyl derivatives of other metals.

At first the thermo reaction of the compound with various organic solvents was studied. For this purpose benzene, methanol, isopropyl alcohol, chloroform, and CCl_4 , were selected. When the alcoholic or benzene solutions of the starting materials were heated in sealed tubes, first carefully rid of atmospheric oxygen, a sharp color change from the original yellow to dark green was observed; this is characteristic of lower valency titanium compound. The literature describes the reduction of compounds of tetravalent titanium electrolytically [6] or by means of $LiAlH_4$, zinc dust, and other reducing agents in non-aqueous media [13].

During the thermal decomposition of $(C_5H_5)_2Ti(C_6H_5)_2$ we could assume the reduction of the organotitanium compound at the expense of split off phenyl radicals.



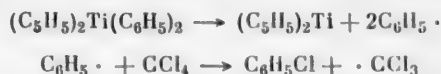
All further experimental data sufficiently confirmed the formation of free phenyl radicals according to equation (1). For instance, the reaction products in solvents agree with the free radical scheme. Decomposition of phenyl radicals in methanolic or isopropanolic media gives benzene and dehydrogenation products of alcohol - formaldehyde or acetone.



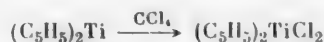
In benzene the phenyl radicals dimerize to diphenyl. The existence of a free-radical reaction is confirmed by the decoloration of the violet α , α -diphenyl- β -picrylhydrazyl added to a benzene or ethanolic solution of $(C_5H_5)_2Ti(C_6H_5)_2$. The color disappearance is rapid when the solutions are heated; slow decoloration also takes place at room temperature.

Bis(cyclopentadienyl) titanium can form on release of phenyl radicals according to reaction (1). According to the literature, the dark green form of the latter is paramagnetic [5]. By the action of hydrochloric acid in the absence of oxygen it is converted to the dichloride $(C_5H_5)_2TiCl_2$. In our case the formation of bis(cyclopentadienyl)titanium was proved by "EPR" spectra, which showed the strong paramagnetism of the substance. In addition, the latter was also converted to the dichloride of bis(cyclopentadienyl) titanium by the action of mercuric chloride and CCl_4 .

In this connection it was interesting to conduct reactions on the decomposition of $(C_5H_5)_2Ti(C_6H_5)_2$ in halogen containing solvents. The fully chlorinated solvent CCl_4 , and chloroform which contains both chlorine and hydrogen, were selected for this purpose. The products of thermal decomposition in CCl_4 were found to be $(C_5H_5)_2TiCl_2$, chlorobenzene, and small quantities of diphenyl, the formation of which can be explained by the following scheme:



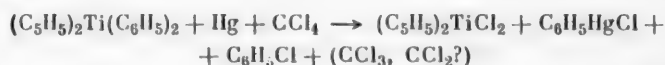
$(C_5H_5)_2TiCl_2$ obviously is obtained via the intermediate bis(cyclopentadienyl) titanium, as demonstrated by reactions in solvents containing no halogen.



Thermo and photo reactions conducted in chloroform showed the formation of dichloride in quantitative yield, benzene, and small quantities of diphenyl. It is interesting to note, that as in the case of diphenylmercury, the phenyl radical takes away hydrogen from the chloroform, and not chlorine [14].



In CCl_4 at 80° homolytic transfer of phenyl radicals to metallic mercury takes place. The formation of phenylmercury chloride according to



is sufficient evidence that there are phenyl radicals present on the surface of metallic mercury. Also, the dichloride of bis(cyclopentadienyl) titanium and chlorobenzene were found among the products of the reaction conducted under stirring in boiling solvent.

The substitution of the phenyl group by chlorine, taking place with the formation of the stable $(C_5H_5)_2TiCl_2$, can occur by other than homolytic processes. For instance, when $(C_5H_5)_2Ti(C_6H_5)_2$ is agitated with dilute hydrochloric acid (1: 1) at room temperature, $(C_5H_5)_2TiCl_2$ and benzene are formed almost quantitatively.



The exchange reaction between bis(cyclopentadienyl) diphenyltitanium and mercuric chloride also proceeds with the formation of bis(cyclopentadienyl) titanium dichloride. The reaction was conducted in CCl_4 or benzene solution at 80°, with stirring in a nitrogen atmosphere. The ratio of initial components was changed from 1: 1 to 1: 2 for $(C_5H_5)_2Ti(C_6H_5)_2 : HgCl_2$; in the latter case the yield of reaction products was greater. The main products isolated were bis(cyclopentadienyl) titanium dichloride and phenylmercury chloride, the ratio of which remained 1: 2. For instance, the reaction of 0.021 mole $(C_5H_5)_2Ti(C_6H_5)_2$ with 0.042 mole $HgCl_2$ produced 0.0145 mole $(C_5H_5)_2$

(C₅H₅)₂TiCl₂ (69%) and 0.0282 mole C₆H₅HgCl (67%). From this we can conclude, that the exchange reaction between bis(cyclopentadienyl)diphenyltitanium and HgCl₂, according to equation (2), is the main reaction.



In benzene solutions the quantities of main products were very different. When 0.0156 mole (C₅H₅)₂Ti(C₆H₅)₂ reacted with 0.0312 mole HgCl₂ in benzene at 80°, the yield was 0.0037 mole (C₅H₅)₂TiCl₂ (24%) and 0.0284 mole C₆H₅HgCl (89%). In addition to the main reaction products from a CCl₄ medium, chlorobenzene, diphenyl, and calomel were also formed. In benzene solution diphenyl and calomel were found. The formation of chlorobenzene and diphenyl is easily explained by the radical reactions of phenyl radicals with the solvent, as described above.

The formation of calomel can be explained by a reaction between bis(cyclopentadienyl)titanium obtained as an intermediate in reaction (1) and mercuric chloride.



Reversible exchange reactions of radical-halogen are characteristic of organometallic compounds. Hence the problem of possible reversible exchange of chlorine for the phenyl radical in the system (C₅H₅)₂TiCl₂ + (C₆H₅)₂Hg. Actually, when the components are heated in methylene chloride or benzene, the reaction is as follows:



All reactions described were conducted in an atmosphere containing no oxygen. In the presence of air sediments containing oxidation products of bis(cyclopentadienyl)titanium were formed. We showed by special experiments, that (C₅H₅)₂Ti(C₆H₅)₂ is oxidized by air in benzene solution to give phenol, diphenyl, and a yellow, amorphous substance which did not dissolve in organic solvents, and which contained the cyclopentadienyl ring, Ti, and oxygen. On oxidation conducted in a CCl₄ medium, it was found that the solvent also participated in the oxidation process. In addition to the oxidation product of the organotitanium compound mentioned above, phosgene, chlorobenzene, and (C₅H₅)₂TiCl₂, were also isolated.

EXPERIMENTAL

Initial products. Cyclopentadiene. For the synthesis we used freshly distilled cyclopentadiene with boiling point: 40-42°, obtained by depolymerization of purified dicyclopentadiene [b.p.: 70° (24 mm)].

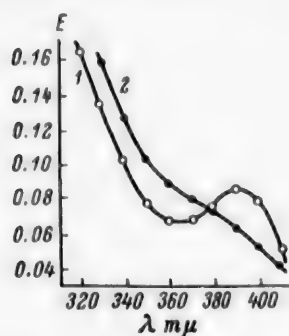
Synthesis of bis(cyclopentadienyl)titanium dichloride. (C₅H₅)₂TiCl₂ was obtained by us by a modified Wilkinson-Birmingham method [6] by reaction of C₅H₅MgCl with TiCl₄. The Grignard reagent was prepared from 21.0 g magnesium and 78.5 g (1.0 mole) isopropyl chloride in 250 ml ethyl ether. To the warm solution was added, dropwise and over a period of 1-1.5 hours 66.0 g (1.0 mole) freshly distilled cyclopentadiene in 100 ml absolute ether. Then the mixture was heated for two hours. To the suspension of C₅H₅MgCl, cooled to -5° and vigorously stirred, was added dropwise and over two hours a solution of 81.7 g (0.43 mole) freshly distilled TiCl₄ in 100 ml absolute xylene. The mixture was kept cool and stirred for another hour, after which it was kept overnight in a cooler. The dark red precipitate which had formed was filtered on a Büchner funnel, washed with ether, and in portion slowly dissolved by small quantities of methanol at -5 to 0°. Heating up of the mixture must be avoided, because then (C₅H₅)₂TiCl₂ could react with methanol. The precipitate thus treated was extracted with chloroform in a Soxhlet apparatus. The yield of recrystallized product was 40-45%, m.p.: 285-287°.

Synthesis of bis(cyclopentadienyl)diphenyltitanium. (C₅H₅)₂Ti(C₆H₅)₂ was prepared by a somewhat modified Summers and Uloth method [11] from bis(cyclopentadienyl)titanium dichloride and phenyllithium. The crude product was treated as above, with cold methanol to avoid the possible complexes with phenyllithium. The yield of (C₅H₅)₂Ti(C₆H₅)₂ in separate experiments reached 90-95%, m.p.: 145-146°, which agrees with literature data.

Thermo reaction of (C₅H₅)₂Ti(C₆H₅)₂ with CCl₄. Five g (0.015 mole) of (C₅H₅)₂Ti(C₆H₅)₂ in 40 ml CCl₄ was heated for eight hours at 60° in a nitrogen atmosphere. The original yellow solution turned red and a dark red precipitate formed. The latter was filtered, and its weight was 3.4 g. In the precipitate 1.9 g (0.0076 mole) of (C₅H₅)₂TiCl₂ was found spectrophotometrically.

The spectrophotometric measurements were done on a quartz SF-4 spectrophotometer. Starting with a special absorption spectrum of $(C_5H_5)_2TiCl_2$ (see graph) with a minimum at λ 360 $m\mu$ and maximum at λ 390 $m\mu$, these regions were selected as analytic. The concentration of $(C_5H_5)_2TiCl_2$ was determined by graduated graphs constructed and calibrated on known, pure samples. The determination of $(C_5H_5)_2TiCl_2$ and $(C_5H_5)_2Ti(C_6H_5)_2$ in their joint presence was done on artificial mixtures and it gave satisfactory results*. $(C_5H_5)_2TiCl_2$ melted at 285° (from toluene). In addition, 0.8 g (0.0024 mole) unreacted $(C_5H_5)_2Ti(C_6H_5)_2$ was determined spectrophotometrically. CCl_4 was distilled from the filtrate at 76-77°. The rest was steam distilled; that gave 0.0032 mole chlorobenzene, which by nitration [15] was converted to 2, 4-dinitrochlorobenzene (0.65 g), m.p.: 44°. A mixed melting point test with a known pure product gave m.p.: 47°. Small quantities of diphenyl (m.p. 69°) were also found. The solid precipitate was steam distilled (1.43 g) and it contained 0.003 gram-atom Ti. No cyclopentadiene was found among the products.

Thermo reaction of $(C_5H_5)_2Ti(C_6H_5)_2$ with chloroform. $(C_5H_5)_2Ti(C_6H_5)_2$ (2.7 g, 0.0081 mole) and 40 ml chloroform was placed in a sealed tube previously carefully evacuated, and heated at 70° for five hours. From the reddening a solution a precipitate of bis(cyclopentadienyl) titanium dichloride was obtained (0.2 g), m.p. 287°. The filtrate was distilled on a steam bath. The distillate was analyzed on an SF-4 spectrophotometer for benzene content. From absorption in the region 245-260 $m\mu$ in the ultraviolet spectrum, 0.005 mole benzene was determined. After distillation of the solvent another 1.75 g $(C_5H_5)_2TiCl_2$, m.p. 287°, was isolated. No melting point depression was observed during a mixed melting point test with a known pure sample. Altogether 1.95 g $(C_5H_5)_2TiCl_2$ or 0.0078 mole was isolated. Also, when the residue was steam distilled, traces of diphenyl were found. No chlorobenzene or cyclopentadiene was found among the reaction products.



Spectrophotometric curves of the dependency of optical density of organotitanium compounds on the wave length. 1) For pure bis(cyclopentadienyl)titanium dichloride; 2) for pure bis(cyclopentadienyl)diphenyltitanium.

Photo reaction of $(C_5H_5)_2Ti(C_6H_5)_2$ with chloroform. $(C_5H_5)_2Ti(C_6H_5)_2$ (2.7 g, 0.0081 mole) and 40 ml $CHCl_3$ was placed in a quartz sealed tube previously carefully evacuated, irradiated with ultraviolet light of a PRK-2 lamp for 50-60 hours. Here a red precipitate of the dichloride formed. Filtration yielded 0.4 g $(C_5H_5)_2TiCl_2$, and concentration of the solution another 1.45 g, m.p. 287° (recrystallized from toluene). Altogether 1.85 g (0.0074 mole) $(C_5H_5)_2TiCl_2$ was isolated. Distillation of the solvent, same as above, led to spectrophotometric determination of 0.004 mole benzene. When the residue was steam distilled and the dichloride of bis(cyclopentadienyl) titanium isolated, 0.1 g diphenyl, m.p. 69°, was isolated. No chlorobenzene or cyclopentadiene was found among the reaction products.

Thermal decomposition of $(C_5H_5)_2Ti(C_6H_5)_2$ in benzene. $(C_5H_5)_2Ti(C_6H_5)_2$ (2.2 g 0.0066 mole) and 20 ml benzene was placed in a sealed tube previously carefully evacuated, and heated at 90° for 10 hours. A sharp color change took place, from the original yellow to dark green. The dark green solution was extremely paramagnetic, as was shown by EPR spectra. When CCl_4 free of atmospheric oxygen was added to the dark green solution *in vacuo*, the color of the solution turned red. Further operations were done in air. The precipitate of $(C_5H_5)_2TiCl_2$ which formed (0.45 g, 0.0018 mole) melted at 285° after recrystallization from toluene. A mixed melting point test with a known pure substance gave no melting point depression. The solution yielded another 0.54 g (0.0022 mole) of dichloride, melting at 285°. Altogether 0.99 g (0.0040 mole) was isolated. After removal of dichloride, steam distillation of the residue gave 0.2 g (0.0013 mole) diphenyl, m.p. 69°. Infrared spectra of distilled solvents showed the absence of chlorobenzene among the reaction products.

Thermo reaction of $(C_5H_5)_2Ti(C_6H_5)_2$ with alcohols. $(C_5H_5)_2Ti(C_6H_5)_2$ (4.0 g, 0.012 mole) and 40 ml CH_3OH was placed in a sealed tube previously carefully evacuated, and heated at 70-75° for four hours. The starting material dissolved and the color turned dark green. The ampule was opened in air, the dark green color vanished gradually, and very rapidly on heating. The solvent was evaporated on a steam bath. The distillate was diluted with water, extracted with CCl_4 , and nitrated. This gave 1.85 g (0.011 mole) m-dinitrobenzene, m.p. 90°. A mixed melting point test with a known sample gave no depression. Formaldehyde was isolated from the water layer after removal of the CCl_4 extract. The dimedon (dimethylcyclohexanedione) derivative of formaldehyde melted at 188°.

* The authors are indebted to N. N. Vyshinskii for the spectrophotometric measurements.

Diphenyl, m.p. 69°, was also obtained. The residue from the solvent removal – a light yellow, transparent liquid of the organotitanium compound – was easily hydrolyzed by water, also by moist air. On steam distillation it decomposed with the formation of cyclopentadiene. The distillate with the characteristic cyclopentadiene odor was extracted with benzene and ether, and dried (all operations at 0°). To the dry solution was added 2.0 g maleic anhydride and the solution allowed to stand for two hours at 0°. Concentration and strong cooling of the solution gave the anhydride of cis-endomethylenetetrahydrophthalic acid, m.p. 160–162° (recrystallized from benzene). A mixed melting point test with a specially prepared derivative of pure cyclopentadiene with maleic anhydride melted at 164°.

4.0 g (0.012 mole) $(C_5H_5)_2Ti(C_6H_5)_2$ in 25 ml isopropanol was heated at 80° in a nitrogen atmosphere for six hours. This gave 0.5 g benzene (m-dinitrobenzene had a m.p. 90°) among the reaction products. Acetone was proved by the formation of 2,4-dinitrophenylhydrazone, m. p. 126°.

Reaction of $(C_5H_5)_2Ti(C_6H_5)_2$ with mercuric chloride in a CCl_4 medium. $(C_5H_5)_2Ti(C_6H_5)_2$ (7.0 g, 0.021 mole) and 11.45 g (0.042 mole) $HgCl_2$ in 40 ml CCl_4 was heated under stirring for eight hours to 70° in a nitrogen atmosphere. The solution reddened and a reddish brown precipitate appeared. The latter was filtered and it weighed 16.78 g. The precipitate was extracted with methylene chloride, and in the extract 3.6 g (69%) $(C_5H_5)_2TiCl_2$, m.p. 283° (from toluene), was determined spectrophotometrically. A mixed melting point test with a known pure substance was 287°. In the same precipitate was found 8.83 g (67%) phenylmercury chloride, m.p. 255° (from acetone), by the Uitmor [16] method. No melting point depression occurred with a known pure substance.

The blackening of a sublimated portion of the precipitate under the effect of concentrated ammonia indicates the presence of calomel. The solvent was distilled off the filtrate at 76–77°. The rest was steam distilled; that gave 0.22 g (0.0014 mole) diphenyl, m.p. 69°, and a small quantity of chlorobenzene, which after nitration was identified as 2, 4-dinitrochlorobenzene, m.p. 43°. The mixed melting point with a known pure substance was 47°.

After steam distillation the precipitate weighed 1.43 g and contained 0.003 gram-atoms titanium. No cyclopentadiene was found among the reaction products. In some cases it was possible to recover partially, from aqueous solutions of residues from the steam distillation, the hydrolyzed $(C_5H_5)_2TiCl_2$ by the action of concentrated hydrochloric acid on slight heating, followed by extraction with methylene chloride. The recovery of pure dichloride of bis(cyclopentadienyl) titanium can be almost complete by the action of steam.

Reaction of $(C_5H_5)_2Ti(C_6H_5)_2$ with mercuric chloride in a benzene medium. $(C_5H_5)_2Ti(C_6H_5)_2$ (5.17 g, 0.0156 mole) and 8.46 g (0.0312 mole) mercuric chloride in 40 ml benzene was heated under stirring for six hours at 75–80° in a nitrogen atmosphere. The solution reddened and a precipitate weighing 11.12 g formed. Analogously to the treatment described above, the precipitate yielded 8.88 g (89%) phenylmercury chloride, m.p. 255°, and 0.92 g (24%) $(C_5H_5)_2TiCl_2$, m.p. 287°, and qualitatively – calomel. The filtrate was distilled. Steam distillation gave 0.12 g (0.0008 mole) diphenyl, m.p. 69°. The solid residue was steam distilled (0.25 g) and contained 0.002 gram-atom titanium.

The formation of bis(cyclopentadienyl) titanium dichloride occurred by the action of mercuric chloride on bis(cyclopentadienyl) titanium [green paramagnetic reaction product of $(C_5H_5)_2Ti(C_6H_5)_2$ and benzene]. The reaction was conducted in the absence of atmospheric oxygen. The dark green color instantly changed to red, which is characteristic of the dichloride. Among the reaction products were $(C_5H_5)_2TiCl_2$, m.p. 285°, and calomel.

Reaction of $(C_5H_5)_2Ti(C_6H_5)_2$ with metallic mercury in a CCl_4 medium. $(C_5H_5)_2Ti(C_6H_5)_2$ (3.8 g, 0.015 mole) and 50 g metallic mercury in 50 ml CCl_4 was heated for nine hours to 80° under vigorous stirring, in a nitrogen atmosphere. The reaction mixture was separated from the mercury, and the latter washed several times with CCl_4 . The organic layer was filtered. The residue (3.45 g) was washed with methanol, and then extracted with boiling acetone. The acetone solution yielded 1.77 g (0.0057 mole) phenylmercury chloride, m.p. 257°. A mixed melting point test with a known pure substance gave 257°. In the filtrate 0.003 mole $(C_5H_5)_2TiCl_2$, m.p. 285°, was determined spectrophotometrically; no melting point depression occurred. The filtrate was steam distilled. The first fraction of the distillate was nitrated. That gave 0.15 g (0.00074 mole) of 2, 4-dinitrochlorobenzene, m.p. 48° (proved by a mixed melting point test with a known pure substance). In addition, the second fraction of the steam distillate yielded 0.1 g (0.00065 mole) diphenyl, m.p. 69°.

Reaction of $(C_5H_5)_2TiCl_2$ with diphenylmercury. $(C_5H_5)_2TiCl_2$ (1.85 g, 0.0074 mole) and 5.24 g (0.0148 mole) diphenylmercury in 70 ml methylene chloride was heated at 35° and stirred in a nitrogen atmosphere for 20 hours. Lustrous leaflets appeared as the precipitate. The reaction mixture was steam distilled. The distillate had a specific odor of cyclopentadiene, and decolorized bromine water. After determination of the iodine number, the quantity of

cyclopentadiene was calculated, as equal to 0.011 mole. The solid residue from the steam distillation weighed 4.75 g. From it was extracted with boiling benzene 0.95 g (0.0027 mole) unreacted diphenylmercury, m.p. 125°. Boiling acetone extracted 3.22 g (0.0103 mole) phenylmercury chloride, m.p. 255°, which represents 85% of the theoretical, based on reacted diphenylmercury. The insoluble precipitate, 0.85 g, evidently is a mixture of TiO_2 and decomposition products of unreacted $(\text{C}_5\text{H}_5)_2\text{TiCl}_2$.

When the same reaction was conducted in a benzene medium at 70° over a period of 24 hours, only 1.0 g (21.6%) phenylmercury chloride, m.p. 255°, was obtained.

Reaction of $(\text{C}_5\text{H}_5)_2\text{Ti}(\text{C}_6\text{H}_5)_2$ with hydrochloric acid. A suspension of 2.0 g (0.006 mole) $(\text{C}_5\text{H}_5)_2\text{Ti}(\text{C}_6\text{H}_5)_2$ in 20 ml HCl (1:1) was shaken for three hours at room temperature in air. The yellow sediment of the initial compound changed to red crystals of bis(cyclopentadienyl) titanium dichloride, the latter in 1.2 g (0.0048 mole) yield, m.p. 287°. The aqueous layer was extracted with CCl_4 and the extract nitrated. This gave 0.65 g (0.0039 mole) of *m*-dinitrobenzene, m.p. 89°.

Oxidation of $(\text{C}_5\text{H}_5)_2\text{Ti}(\text{C}_6\text{H}_5)_2$ in CCl_4 . $(\text{C}_5\text{H}_5)_2\text{Ti}(\text{C}_6\text{H}_5)_2$ (4.0 g, 0.012 mole) in 40 ml CCl_4 was heated for 25 hours at 45–55° in a stream of dry oxygen. Preliminary tests showed the presence of phosgene among the reaction products. When the gaseous reaction products were passed through aniline water, long needles of diphenylurea crystals, m.p. 189°, formed. The quantity of phosgene was determined by absorption in alkali solutions. We found 0.0019 gram-ion CO_3^{--} , which corresponds to 0.0019 mole phosgene. Heating precipitated 3.4 g of a sediment. Fractional crystallization of the sediment in methylene chloride yielded 1.28 g (0.0051 mole) $(\text{C}_5\text{H}_5)_2\text{TiCl}_2$, m.p. 283°. The rest – amorphous, insoluble yellow sediment – evidently is an oxidation product of the organotitanium compound. Steam distillation of the filtrate gave chlorobenzene, which was nitrated to 2, 4-dinitrochlorobenzene. The weight of the latter was 0.11 g (0.00054 mole), m.p. 44°. Iodometric titration also determined 0.0003 mole phenol (tribromophenol, m.p. 96°) and traces of diphenyl.

Oxidation of $(\text{C}_5\text{H}_5)_2\text{Ti}(\text{C}_6\text{H}_5)_2$ in benzene. $(\text{C}_5\text{H}_5)_2\text{Ti}(\text{C}_6\text{H}_5)_2$ (3.64 g, 0.011 mole) in 40 ml C_6H_6 was heated at 60° for 20 hours in a stream of dry air. A yellow precipitate formed, 0.98 g, which did not dissolve in organic solvents. The substance had the following composition in %: C 44.43; O 26.82; H 4.45; Ti 24.30. It was not possible to ascribe a formula of an individual compound to it.

Among the reaction products phenol and diphenyl (m.p. 69°) were also found. The phenol was identified from tribromophenol, m.p. 96°.

SUMMARY

1. When bis(cyclopentadienyl) diphenyltitanium is heated, it splits off phenyl radicals which further react according to the usual radical scheme. Thus, they break away hydrogen from alcohols and chloroform, chlorine from CCl_4 , and dimerize in a benzene medium. Phenyl radicals in CCl_4 solution can be fixed by metallic mercury.
2. Bis(cyclopentadienyl) titanium is quite stable in benzene or alcohol solutions, but easily converts to the dichloride, breaking off chlorine from CCl_4 or mercuric chloride. In the presence of oxygen it gives amorphous sediments of oxide derivatives of bis(cyclopentadienyl) titanium.
3. Bis(cyclopentadienyl) diphenyltitanium reacts with mercuric chloride in a CCl_4 medium by exchanging chlorine for phenyl, with the formation of dichloride and phenylmercury chloride. This heterolytic reaction goes to an extent of about 70%; the free radical reaction with the solvent proceeds in a parallel way. The reversible exchange of chlorine for phenyl radicals occurs on heating of bis(cyclopentadienyl) titanium dichloride with diphenylmercury.

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FREE RADICAL REACTIONS IN SOLUTIONS

XVIII. THE RELATIVE ACTIVITY OF FREE $\text{CH}_3\cdot$ AND $(\text{CH}_3)_3\text{CO}\cdot$ RADICALS IN THE REMOVAL OF AN H ATOM FROM HYDROCARBONS

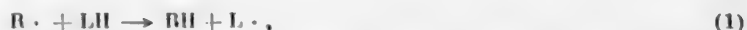
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Examination of the literature data on the activity of free radicals containing an unpaired electron at the oxygen atom and hydrocarbon free radicals in the reaction



leads to the conclusion that radicals of the first type have a relatively greater reactivity. This conclusion is supported, for example, by the relatively low heat of activation found for the reaction



which, according to Wijnen, is 4.5 kcal/mole [1]. Values of 10.0 [1] and 9.7 kcal/mole [2] are reported for the similar reaction of the $\text{CH}_3\cdot$ radical. The great activity of $\text{RO}\cdot$ and $\text{ROO}\cdot$ radicals in reaction (1) is also indicated by their great ability to detach an H atom from unsaturated compounds which react with hydrocarbon free radicals preferentially at the double bond. These results were obtained in particular in a study of the reaction of the $\text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{O}\cdot$ radical with 1-pentene, isobutylene, and isoprene [3]. Other publications [4, 5] refer to the great tendency of radicals of this type to react mainly according to reaction (1). At the same time no investigations have been reported in which the study of the concurrent reactions



for the $\text{C}\cdot$ radicals might have been carried out under comparable conditions. For our investigation we selected $\text{CH}_3\cdot$ and $(\text{CH}_3)_3\text{CO}\cdot$ free radicals which were derived from methylphenyltriazenes and ditertiary butyl peroxide:

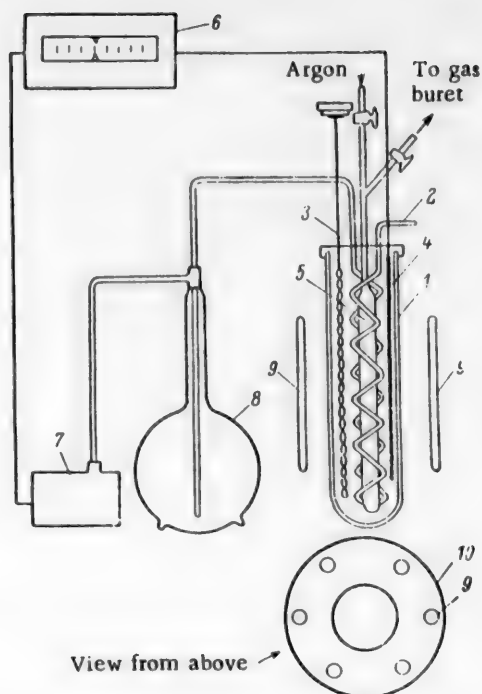


These compounds were decomposed photochemically in various hydrocarbons in the -60 to 20° temperature region.

Photolysis of ditertiary butyl peroxide in the liquid phase was studied by other authors in the absence of solvent at 17° [6] and in carbon tetrachloride solution at room temperature [7]. The hydrocarbons were used merely as a medium for thermal decomposition of ditertiary butyl peroxide [8, 9]. Methylphenyltriazenes, whose thermal decomposition has been repeatedly used for generation of $\text{CH}_3\cdot$ radicals [10], has not previously been subjected to photolysis.

EXPERIMENTAL

The apparatus illustrated in the figure was used for photolysis. The ampoule containing the solution of triazene



Set-up of photolysis apparatus. 1) Quartz Dewar flask; 2) cooling coil; 3) stirrer; 4) potentiometer; 5) reaction ampoule; 7) air blower; 8) metal Dewar flask; 9) PRK-4 lamps; 10) copper cylinder.

or peroxide was placed in an unsilvered Dewar flask 1 of fused quartz which was filled with dry isopentane and closed by a rubber stopper with openings for cooling coil 2, stirrer 3, thermocouple 4, and reaction ampoule 5. The latter was connected to a gas buret. A constant temperature (to within $\pm 1^\circ$) was maintained in the ampoule with the help of a PSR-1P6 potentiometer connected to a recording thermocouple 4 and a blower 7. The cooling agent was liquid nitrogen which was injected from a metal Dewar vessel 8 under pressure, created by the blower, into coil 2 at the instant of connection of the potentiometer relay. Water was used as the thermostating medium in experiments carried out at 20° . Radiation was supplied by six PRK-4 lamps 9 fixed vertically at the inner surface of copper cylinder 10 which was covered with magnesia. The distance between the axes of the lamps and the ampoule was 6 cm. These conditions permitted the attainment of a considerable degree of decomposition of the free radical sources with relatively short exposures.

Photolysis of methylphenyltriazene and ditertiary butyl peroxide was carried out in an argon atmosphere. At the conclusion of the triazene photolysis experiments, dissolved methane was separated by blowing argon (100-150 ml) through the solution. This argon was collected in the same buret. It was shown in blank experiments that this procedure insures complete elimination of the methane formed during photolysis. The gas was analyzed in VTI-2 apparatus. The degree of decomposition of the triazene was determined from the quantity of nitrogen evolved during decomposition of a sample (taken from the reaction mixture after photolysis) with excess of 25% solution of acetic acid in isopropylbenzene. It is known [11] that acidic de-

composition of triazenes leads to quantitative releases of nitrogen. The total yield of nitrogen released during photolysis of the triazene and during acid decomposition of the reaction mixture at the end of the experiments was 97-99% of the theoretical amount.

Determination of the undecomposed peroxide and of the alcohol and acetone formed on photolysis was effected with the help of infrared spectroscopy. The infrared absorption spectra were obtained with a two-beam IKS-14 spectrophotometer, using LiF and NaCl prisms, in the 4000 to 700 cm^{-1} region. Cells were used with layer thicknesses of 0.009 to 0.2 cm depending on the solvent and the concentrations of peroxide and photolysis products. Absorption coefficients were determined by taking the spectra of specially prepared standard concentrations of peroxide, acetone, and alcohol separately in each solvent, and of their ternary mixture. In the determination, for example, of an artificial mixture in 1-heptene which had contained 0.050 mole/liter peroxide, 0.303 mole/liter tertiary butyl alcohol, and 0.020 mole/liter acetone, the amounts of the respective substances found were 0.149 , 0.302 , and 0.025 mole/liter*. The content of peroxide was determined with the help of the 875 cm^{-1} absorption band, that of tertiary butyl alcohol with the 3360 or 3420 cm^{-1} band, and that of acetone with the 1720 cm^{-1} band.

For comparison of the activity of $\text{CH}_3\cdot$ and $(\text{CH}_3)_3\text{CO}\cdot$ radicals in the concurrent reactions (3a) and (3b), we selected the photochemical method of decomposition of the respective substances in order to insure an identical temperature during decomposition of the two sources of free radicals and in order to be able to carry out this process at a sufficiently low temperature. The latter requirement was desirable for evaluation of the behavior of radicals containing an unpaired electron at the oxygen atom. In the case of free alkyl radicals it is known that lowering of temperature leads to preferential addition at the double bond (3b) rather than to detachment of the H atom (3a). This is illustrated, for example, by the results of Szwarc [12] for methyl free radicals. It could be expected that the marked lowering of temperature during generation of free radicals of the $\text{RO}\cdot$ type in a medium of unsaturated hydrocarbon would also create the most favorable conditions for reaction (3b).

* The error of 0.005 mole/liter is associated in this case with the low optical density at 1700 cm^{-1} .

Photolysis of Methylphenyltriazene

The main products of thermal decomposition of methylphenyltriazene in cumene are methane, methylaniline, and aniline [13]. Blank experiments showed that under the conditions of photochemical decomposition of methylphenyltriazene, aniline and methylaniline underwent further changes which made the determination of their true yield impossible. We therefore limited ourselves to determining the quantity of methane formed by the reaction:



Performance of photochemical decomposition of methylphenyltriazene over a wide temperature range enabled data to be obtained that characterize the change of relative activity of the $\text{CH}_3\cdot$ radical as a function of the temperature (Table 1). It was established in special experiments that the degree of triazene decomposition does not influence the methane yield at a given temperature (Table 2).

TABLE 1. Photolysis of Methylphenyltriazene in Isopropylbenzene and in 1-Heptene (Duration of Experiments 4-6 hr)

Expt. No.	Solvent	Concentration of methylphenyltriazene (in % of init. sub.)	Temp.	Degree of decomposition of methylphenyltriazene (in % of init. sub.)	Yield of methane (in % of theory)
1	Isopropylbenzene	5.2	20°	68.8	23.3
2				69.3	21.0
3		5.2	-20	32.6	13.0
4				30.1	13.7
5		5.2	-40	32.6	9.2
6				40.0	9.3
7		5.2	-60	35.5	7.4
8				38.4	7.5
9	1-Heptene	4.2	20	70.7	9.8
10				73.1	10.2

TABLE 2. Yield of Methane During Photolysis of Methylphenyltriazene in Isopropylbenzene at 20°

Expt. No.	Concentration of methylphenyltriazene (in mole %)	Degree of decomposition of methylphenyltriazene (in % of init. sub.)	Yield of methane (in % of theoretical)
11	1.2	18.0	21.2
12	1.2	29.0	22.8
13	1.2	49.5	20.7
2	5.2	69.3	21.0

It was shown in the paper cited above [13] that the yield of methane in thermal decomposition of methylphenyltriazene in isopropylbenzene at 110° is 56% of the theoretical. Under photolytic conditions at 20° the yield falls to 21-23%, and at -60° it falls to 7.5% of the theoretical. This sharp fall in methane yield is not associated with recombination of $\text{CH}_3\cdot$ radicals, which ought to have led to formation of ethane, since the gas evolved during photolysis of methylphenyltriazene contains only methane and nitrogen. The conclusion to be drawn is therefore that the falling methane yield with falling experimental temperature is associated with an increased yield of methylaniline. This could not be experimentally confirmed for the reasons mentioned above.

It was shown that the methane yield from photochemical decomposition of methylphenyltriazene in 1-heptene at 20° is one-half of that in isopropylbenzene. This suggests predominance of reaction (3b) (Table 1) in the former solvent. A similar observation was made earlier in a study of the thermal decomposition of methylphenyltriazene in the same medium [14, 15]. It was also established [16] that the fall in yield of methane is associated with formation of products of addition of $\text{CH}_3\cdot$ radicals to 1-heptene.

We also demonstrated the appreciable increasing participation of the reaction of addition of $\text{CH}_3\cdot$ radicals to the double bond with falling temperature in the system α -methylstyrene – isopropylbenzene. It is known [14] that thermal decomposition of methylphenyltriazene in α -methylstyrene is accompanied by quantitative addition of methyl radicals to the double bond; methane is then not formed at all. In the thermal decomposition of methylphenyltriazene in isopropylbenzene, methane formation is (as noted above) the main conversion reaction of methyl free radicals. We selected the system α -methylstyrene – isopropylbenzene as the reaction medium in 1 : 9 molar ratio. In this case the two reactions proceed side by side: detachment of an H atom from isopropylbenzene and addition of $\text{CH}_3\cdot$ radicals to α -methylstyrene. Data obtained in thermal decomposition of methylphenyltriazene at 110° and during its photolysis at 20° in this two-component solvent are set forth in Table 3. Here, as with 1-heptene, falling temperature leads to a sharp drop in methane yield, which indicates a corresponding increase in the relative participation of reaction of $\text{CH}_3\cdot$ radicals with α -methylstyrene.

TABLE 3. Decomposition of Methylphenyltriazene in the System α -Methylstyrene – Isopropylbenzene (Molar Ratio of Hydrocarbons 1 : 9. Concentration of Methylphenyltriazene 5 mole-%)

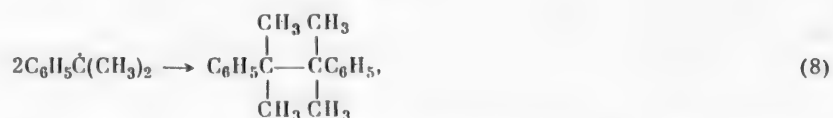
Expt. No.	Conditions of decomposition	Degree of decomp. (in % of init. sub.)	Yield of methane (in % of theoretical)
14	Thermal decomposition at 110°	99.7	8.3
15		100.0	9.5
16	Photolysis at 20°	60.5	2.2
17		56.0	2.1

Photolysis of Ditertiary Butyl Peroxide

As noted above, the decomposition of ditertiary butyl peroxide in a hydrocarbon medium has been studied only under conditions of thermal breakdown. In a study of this process in isopropylbenzene at 125 – 145° it was shown [8] that the main conversion products are tertiary butyl alcohol and acetone. We studied the products of photochemical breakdown of ditertiary butyl peroxide in isopropylbenzene at 20 and -60° (Table 4). In both cases tertiary butyl alcohol is formed quantitatively due to the reaction:



Free $\text{C}_6\text{H}_5\dot{\text{C}}(\text{CH}_3)_2$, formed in reaction (7), recombine to give dicumyl:



which is isolated in a yield of about 90% of the theoretical. We did not detect the breakdown of the tertiary butoxy radical under our conditions in isopropylbenzene. This breakdown has often been observed in the decomposition of ditertiary butyl peroxide and leads to acetone and free methyl radicals:



The features of the behavior of the $(\text{CH}_3)_3\text{CO}\cdot$ radical become more intelligible in the light of the results obtained in a study of the products of photolysis of ditertiary butyl peroxide in 1-heptene. Contrary to what is observed with the $\text{CH}_3\cdot$ radical, for which the yield of methane in 1-heptene falls sharply in comparison with that in isopropylbenzene due to the double-bond reaction (3b), such an effect is not observed. Just as in isopropylbenzene, the yield of tert. butyl alcohol in 1-heptene [calculated on the undecomposed $(\text{CH}_3)_3\text{CO}\cdot$ radicals] is quantitative. Reduction in temperature to -60° does not lead to a change in the effect noted. The sole difference in behavior observed during photolysis in 1-heptene is formation of a small quantity of acetone due to reaction (9). Under our conditions the quantity of acetone did not exceed 4% of the theoretical (Table 4).

TABLE 4. Main Products of Photolysis of Ditertiary Butyl Peroxide in Various Media (Duration of Experiments 1-3 hr)

Expt. No.	Solvent	Concentration* of ditert. butyl peroxide (in moles)	Temp.	* of decomp. of ditert. butyl peroxide in % of init. sub.	Yield %	
					tert. butyl alcohol	acetone
18	Isopropylbenzene	2.0	20°	44.0	100.0	0
19		2.0		50.0	100.0	0
20		1.0	-60	30.0	98.4	0
21		2.0		25.0	100.0	0
22	1-Heptene	5.0	20	60.6	97.9	4
23		5.0		54.0	94.0	4
24		5.0	-60	45.4	94.7	4
25		5.0		58.0	98.1	3
26	Benzene	1.0	20	46.6	0	35
27		0.7		20.0	0	41
28	Isoprene	8.0	20	30.0	0	3-4
29		8.0		29.6	0	3-4

* The difference in peroxide concentration during photolysis in the different media is associated with the convenience of operation of the spectroscopic analysis.

The results obtained in photolysis of ditertiary butyl peroxide in 1-heptene indicate complete absence of addition of $(\text{CH}_3)_3\text{CO}\cdot$ radicals to the olefinic vinyl group down to -60° .

We established the complete absence of hydrogen detachment reaction with tert. butoxyl free radicals during photolysis of ditertiary butyl peroxide in a medium of benzene and isoprene (Table 4). In the case of benzene this phenomenon is evidently associated not only with the great stability of the C-H bond but also with the inability of benzene to react with $(\text{CH}_3)_3\text{CO}\cdot$ radicals by a two-step mechanism (addition to the aromatic ring followed by detachment of the labile hydrogen atom), which had been established in the case of the $\text{CH}_3\cdot$ radical by Szwarc [12]. The main reaction with $(\text{CH}_3)_3\text{CO}\cdot$ radicals in the present case is their decomposition (reaction 9). The disproportion between the degree of peroxide decomposition and the acetone yield must be attributed to its partial photolysis. We selected isoprene as an extremely active free radical acceptor which also contains fairly mobile hydrogen atoms. The non-appearance of tert. butyl alcohol after decomposition of peroxide in isoprene indicates that tert. butoxyl free radicals react only with the double bonds of dienes. Due to the relatively high concentration of free radicals under our experimental conditions, the formation only of low-molecular products of condensation of isoprene was observed.

EXPERIMENTAL

Methylphenyltriazene was synthesized from methylmagnesium iodide and phenyl azide by the Dimrot method [11]. M.p. $36.5-37.5^\circ$ (from hexane); the literature reports m.p. 38° [11]. Ditert. butyl peroxide was synthesized by oxidation of tert. butylsulfuric acid with hydrogen peroxide by the known procedure [17]. B.p. 38° (50 mm), n_D^{20} 1.3890; the literature gives b.p. 40° (55 mm), n_D^{20} 1.3890 [18]. 1-Heptene was prepared from butylmagnesium bromide and allyl bromide [19]; it was fractionated after distillation over sodium. B.p. $94.3-94.7^\circ$ (778 mm), n_D^{20} 1.4002; literature data [19]: b.p. $93.5-93.6^\circ$ (760 mm), n_D^{20} 1.4000. Isopropylbenzene and benzene were purified with sulfuric acid, washed with water, dried over calcium chloride, and distilled over sodium in an argon stream. α -Methylstyrene was washed free of stabilizer with 5% alkali solution, dried over calcium chloride, and distilled in an argon stream. Rectified isoprene was distilled immediately before an experiment. The experimental procedure was described above. We now give data for some typical experiments.

Exp. 8. Irradiation of 0.7101 g of methylphenyltriazene in 13.9 ml of isopropylbenzene was effected at -60° for 6 hr. The volume of gas evolved was 46.4 ml (NTP). The methane content of the gas was 3.40 ml (7.5%). Acidic decomposition of 3 ml of reaction mixture after photolysis with a five-fold excess of 25% acetic acid solution in isopropylbenzene led to evolution of 15.9 ml of nitrogen (NTP). The total yield of nitrogen evolved during photolysis and acidic decomposition of the reaction mixture (calculated on the total volume) was 115.3 ml (NTP), equivalent to 97.8% of the theoretical.

Exp. 17. Irradiation of 0.7105 g of methylphenyltriazene in a solution containing 12.5 ml of isopropylbenzene and 1.4 ml of α -methylstyrene was carried out for 3.5 hr at 20°. The volume of gas given off was 65.2 ml (NTP). The methane content of the gas was 1.4 ml (2.1% of the theoretical). Acidic decomposition of 3 ml of reaction mixture yielded 52 ml of nitrogen (NTP). Total yield of nitrogen 115.8 ml (NTP) or 98.1% of theory.

Exp. 18 . Irradiation of 0.3159 g of di-tert. butyl peroxide in 12.9466 g of isopropylbenzene (peroxide concentration 0.1405 mole/liter) was effected for 1 hr at 20°. The peroxide concentration after irradiation was 0.0787 mole/liter, corresponding to the decomposition of 44.0% of the initial substance. The concentration of tert. butyl alcohol was 0.1236 mole/liter (100% of theory). Acetone was not detected in the mixture.

Exp. 25 . Irradiation of 0.4360 g of di-tert. butyl peroxide in 5.5683 g of 1-heptene (peroxide concentration 0.3490 mole/liter) was carried out for 3 hr at -60°. The peroxide concentration after irradiation was 0.1466 mole/liter. The amount of original peroxide decomposed was 58%. The concentration of tert. butyl alcohol was 0.3970 mole/liter (98.1% of theory). The acetone concentration was 0.0120 mole/liter (3.0% of theory).

Exp. 29 . Irradiation of 1.0940 g of di-tert. butyl peroxide in 5.8764 g of isoprene (peroxide concentration 0.750 mole/liter) was carried out for 2 hr at 20°. The concentration of peroxide after irradiation was 0.528 mole/liter; 29.6% of the initial amount was decomposed. Tert. butyl alcohol was not detected. The acetone concentration was 0.01-0.02 mole/liter (yield up to 4%). After the excess isoprene and undecomposed peroxide had been distilled off, there was isolated 1.60 g of colorless oil from the reaction mixture. This was a mixture of compounds formed during reaction of isoprene (A) with tert. butoxyl radicals (R). In compositions and molecular weight this corresponded most closely to the compound RA_4R .

Found %: C 79.22, 79.29; H 13.59, 13.79. M 401, 396. $C_{28}H_{50}O_2$. Calculated %: C 80.40; H 11.95; O 7.65. M 418.

In a blank experiment it was established that irradiation of isoprene under the same conditions but in the absence of peroxide does not lead to its polymerization.

SUMMARY

On the basis of a study of the products of photolysis of methylphenyltriazene and tert. butyl peroxide in various hydrocarbons, the relative activities of $CH_3\cdot$ and $(CH_3)_2CO\cdot$ radicals were compared in the 20 to -60° region.

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THE PROBLEM OF TRANS-ENOLIZATION

II. THE INFLUENCE OF SOLVENTS ON THE TRANS-ENOLIZATION OF α -ALKYLACETOACETIC ESTERS

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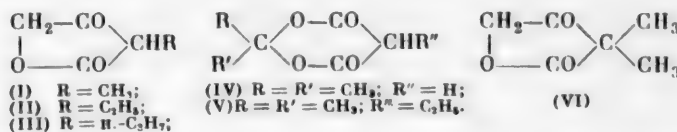
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In the first part of the present investigation [1] we studied the influence of the solvent on the enolization of "trans-fixed" ketoenols. It was shown that enolization of α -alkyltetronic acids is substantially not influenced by the solvent.



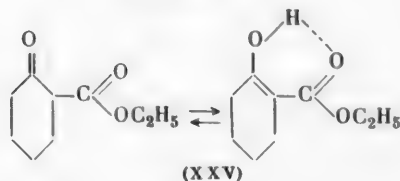
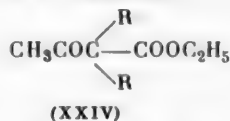
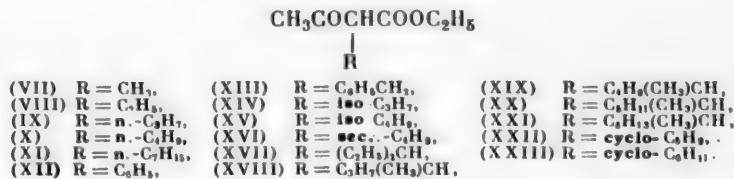
Cyclic acetals of malonic acid - isopropylidene malonate (IV) and isopropylideneethyl malonate (V) - are not enolized at all in the crystalline state in solutions. These conclusions were reached by comparing the UV and IR spectra of these substances with the spectra of the model lactone (VI) which had a ketonic structure.

In the course of evaluation of these regularities of trans-enolization, the question arose of the influence of the solvent on the enolization of ketoenols with an open chain and of the applicability of the formulas (1) and (2) for establishment of the keto-cis-trans-enol equilibrium constants.

$$K_T = EL + E'L' \quad (1)$$

$$K_T = EL + E_1 \quad (2)$$

A study was accordingly made in the present work of the enolization of α -alkylacetoacetic esters containing various alkyl groups (VII-XXIII).



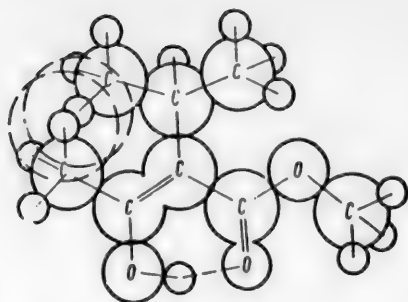


Fig. 1. Cis-enol form of α -isopropylacetoacetic ester.

In this series of derivatives, the members containing branched alkyl groups as substituents are characterized by the fact that formation of a plane cis-enol form with an intramolecular hydrogen bond is accompanied by development of great steric hindrance associated with overlapping of the spheres of action of the α -alkyl and γ -methyl groups. This effect is illustrated roughly in Fig. 1. Enolization of such substances leads exclusively or predominantly to trans-enol forms (compare Henecka [2]).

Enolization of α -alkylacetoacetic esters with branched substituents was studied by spectral and bromometric methods. Enolization of the remaining substances was studied by the bromometric method. In the evaluation of the infrared data of these compounds, special attention was paid to the correct assignment of the frequencies of the various tautomeric forms: ketonic, and cis- and trans-enolic.

The spectra of α,α -disubstituted derivatives of acetoacetic ester (XXIV), which are "fixed" ketonic forms, contain two strong bands in the 1710 - 1730 and 1740 - 1760 cm^{-1} regions which are associated with the valence vibrations of the carbonyl and carbalkoxyl $\text{C}=\text{O}$ groups respectively [3]. The spectra of cis-fixed ketoenols, for example esters of cyclohexanone- (or cyclopentanone-) carboxylic acid (XXV), contain four bands in the 1600 - 1800 cm^{-1} region [4]. Two bands occur in the 1710 - 1730 and 1740 - 1760 cm^{-1} regions and they characterize the ketonic isomer. The two other bands - in the 1610 - 1630 and 1650 - 1660 cm^{-1} regions - evidently belong to the enolic form since their intensity increases with increasing enolizing ability of the solvent while at the same time the intensity of the ketonic form bands decrease [4-6]. The weaker absorption band in the 1610 - 1630 cm^{-1} region is associated with the valence vibration of the $\text{C}=\text{C}$ bond, and the strong band at 1650 - 1660 cm^{-1} is associated with the valence vibration of the $\text{C}=\text{O}$ carbalkoxyl group which participates in development of the intramolecular hydrogen bond and is conjugated with the double bond.

The infrared spectra of the investigated α -alkylacetoacetic esters (Fig. 2) contains three bands in the 1600 - 1750 cm^{-1} region whose frequencies and relationships are set forth in Table 1.

The absence of absorption bands in the 1650 - 1750 cm^{-1} region, characteristic of cis-configuration of molecules, is evidence of the trans-enolization of these compounds. The lack of a marked color reaction with ferric chloride confirms the trans-configuration of the enolic forms. The individual absorption bands corresponding to the $\text{C}=\text{O}$ of the enolic forms are not observed in the spectra. These bands are probably located in the 1700 - 1730 cm^{-1} region and are masked by the strong absorption bands of the ketonic forms. The amount of the latter present, judging by the bromometric determination, considerably exceeds the content of enolic forms.

The good solubility of α -alkylacetoacetic esters in many solvents permitted us to carry out quantitative measurements and to clarify the influence of solvents on the enolization of these compounds.

As was shown earlier in the case of ethyl acetoacetate [4], within the limits of experimental accuracy, solvents do not influence the ratio of the molar coefficients of absorption of the tautomeric forms. In this case the ratio of the optical densities of the absorption bands of the two tautomeric forms in the infrared spectra of the solutions is proportional to the tautomeric equilibrium constant. On the ordinates of Fig. 3 are plotted the ratios of the optical densities ($D_{\text{III}}/D_{\text{II}}$) of the bands of the enolic and ketonic forms (Table 1), while on the abscissas are plotted the constants of L of enolizing ability of solvents as reported by Meyer [7]. We see from Fig. 3 that the content of enolic forms in α -alkyl derivatives of acetoacetic ester containing branched alkyl groups is substantially independent of the solvent. This harmonizes well with the data of ultra-

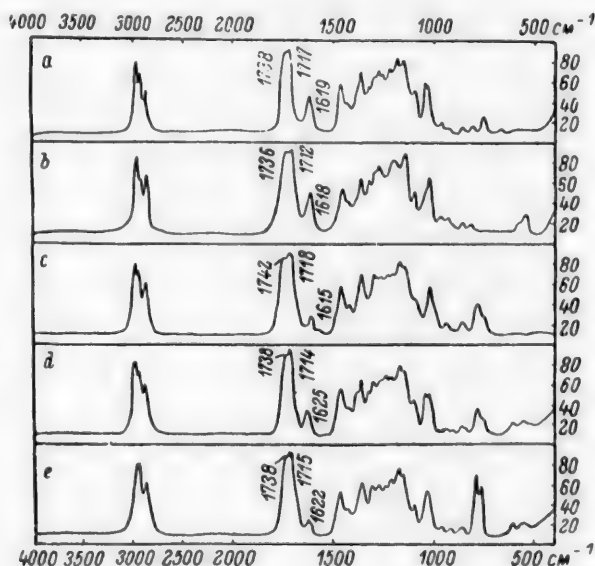


Fig. 2. Infrared spectra of α -alkylacetoacetic esters. Explanation in Table 1.

TABLE 1. Assignment of Frequencies in the 1600-1800 cm^{-1} Region to the Vibrations of the C=O and C=C Bonds of the Tautomeric Forms of α -Alkylacetoacetic Esters

Substituent R in $\text{CH}_3\text{COCHCOOC}_2\text{H}_5$ R	Frequencies (cm^{-1})		
	ketonic form		enol form
	carbonyl (I) ν C=O	carbonyl (II) ν C=O	(III) ν C=C
a) <i>sec</i> - C_4H_9	1738	1717	1619
b) <i>cyclo</i> - C_5H_9	1736	1712	1618
c) $\text{C}_3\text{H}_7(\text{CH}_3)\text{CH}$	1742	1718	1615
d) $(\text{C}_2\text{H}_5)_2\text{CH}$	1738	1714	1625
e) $\text{C}_4\text{H}_9(\text{CH}_3)\text{CH}$	1738	1715	1622

violet spectra which provided information about the influence of solvents with such diverse polarities as water, alcohols, ether, and hexane. In Fig. 4 are plotted the ultraviolet spectra of solutions of α -*sec*. butylacetoacetic ester (XVI) in acidified 67% aqueous methanol (pH 2.5), methanol, ethanol, ether, and hexane. All the curves are similar in intensity ($\epsilon \sim 2000$) and have a maximum in the 233-240 $m\mu$ region. Consequently the *trans*-enolization of open-chain ketoenols (in the case at least of α -alkyl-substituted acetoacetic esters) does not depend on the nature of the solvent, i.e. does not conform to the Meyer law or to the hypothesis of Arndt-Eistert or Geiss.

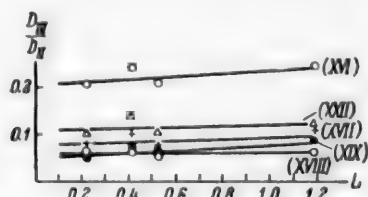


Fig. 3. Ratio of optical densities of enolic and ketonic forms of α -alkylacetoacetic esters, containing branched substituents as a function of L . The numbers in brackets relate to the individual substances.

The spectral results are in full accord with the data of direct brometric determination of the content of enolic forms in the various α -alkylacetoacetic esters. All the investigated substances are extremely weak acids, and the direct bromometric method here gives trustworthy results. The results are set forth in Table 2-4 which contain data not only for esters with branched substituents but also for esters with other alkyl and aryl substituents.

Characteristic of esters with branched alkyl substituents (XVI-XXII) is the well-known constancy of the bromine requirement in various solvents in the absence of color reaction with ferric chloride (Table 4). This confirms the constancy of constant L' of formula (1) for the *trans*-enolization of α -substituted acetoacetic esters, and consequently the applicability of formula (2) to quantitative study of the keto-cis-*trans*-enol equilibrium of these substances. Consequently the doubts expressed in this connection by Eistert and Geiss [8] are no longer valid.

In Figs. 5-7 K_T is plotted as a function of Meyer's L for these substances. Substantially linear plots were obtained in all cases in agreement with formula (2). The slope of the straight line is very small for compounds with branched alkyl substituents. It rises on transition to unbranched alkyls, reaches a value of 45° in ethyl acetoacetate (reference substance), and a still higher value in α -phenylacetoacetic ester. On the basis of the data obtained we calculated from formula (2) the constants E and E_1 and the percentage content of *cis*-enol forms in the enolic fraction of the ketoenols. Results are set forth in Tables 4 and 5.

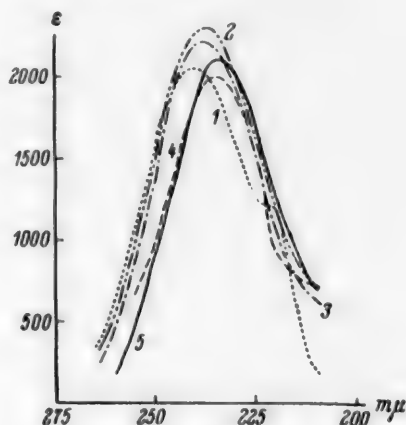


Fig. 4. Ultraviolet spectra of α -*sec*. butylacetoacetic ester. 1) in 67% aqueous methanol at pH 2.50; 2) in methanol; 3) in ethanol; 4) in hexane; 5) in ether.

TABLE 2. Enolic Content of α -Substituted Acetoacetic Esters in Various Solvents

Substituent R in $\text{CH}_3\text{COCHR}-\text{COOC}_2\text{H}_5$	Enolic content (%) in different solvents					
	67% methanol	methanol	ethanol	benzene	ether	carbon tetrachlo- ride
C_2H_5	0.9	1.8	2.8	4.2		
n- C_3H_7	1.9	3.0	4.2	5.6		
n- C_4H_9	3.4	4.3	5.4	6.2		
n- C_7H_{15}	3.6	4.9	6.0	7.0		
iso- C_3H_7	2.6	3.0	3.1	3.6		
iso- C_4H_9	3.3	4.7	6.7	7.9		
sec- C_4H_9	14.3	14.5	13.9	14.6		14.8
$(\text{C}_2\text{H}_5)_2\text{CH}$	6.2	6.7	7.2	8.0	9.3	
n- $\text{C}_3\text{H}_7(\text{CH}_3)\text{CH}$	3.9	4.1	4.3	5.1	6.1	7.2
n- $\text{C}_4\text{H}_9(\text{CH}_3)\text{CH}$	4.5	4.7	4.8	4.9	5.8	6.2
n- $\text{C}_5\text{H}_{11}(\text{CH}_3)\text{CH}$	3.8	3.9	4.1	4.4		
n- $\text{C}_6\text{H}_{13}(\text{CH}_3)\text{CH}$	3.9	4.5	4.4	4.7		
Cyclohexyl	1.7	1.6	2.3	3.1		
Cyclopentyl	10.9	11.7	11.7	12.1		11.6
$\text{C}_6\text{H}_5\text{CH}_2$	1.6	3.2	5.0	7.9		

TABLE 3. Content of Enol in α -Substituted Acetoacetic Esters

Substituent R in $\text{CH}_3\text{COCHCOOC}_2\text{H}_5$ R	Content of enol (%) in solvent									
	67% methanol	acetic acid	methanol	chloro- form	ethanol	ethyl acetate	benzene	toluene	ether	carbon tetra- chloride
H	2.0	5.7	7.1	8.3	11.4	13.0	18.3	21.0	29.1	34.6
CH_3	1.1		2.5		3.9	4.0	5.2	9.0		
C_6H_5	8.4	22.5	19.0	32.0	26.0	40.1	51.5	56.1		68.9

CONCLUSIONS

On the basis of the two parts of the present investigation we may arrive at the conclusion that the influence of a solvent on trans-enolization depends to an appreciable extent on the nature of the keto-enol forming the trans-enol. In this connection ketoenols may be grouped under several headings.

1. Cyclic β -diketones (of the type of dimedon) containing both of the carbonyl groups in the ring. These substances have been thoroughly investigated spectrally by Eistert and co-workers, and their behavior is the opposite of that reported by Meyer: In hydrophilic solvents the enolic (naturally trans) form predominates; in hydrophobic solvents the ketonic form appears. The Meyer law is not valid, but the hypothesis of Eistert and Geiss is valid.

2. Cyclic β -ketolactones of the type of α -alkyltetronic acids. Here we observe approximate constancy of the content of enolic (trans) form in different solvents. Ethereal solvents (ether, dioxane) slightly increase the enolic content, evidently because in these solvents only the enolic (trans) form is capable of forming hydrogen bonds with the ethereal oxygen atoms of the solvent. Hydrogen bonds are formed in hydroxyl-containing solvents both by the ketonic form (with the OH groups of the solvent) and by the enolic form. Judging by the experimental results, this ability of both forms changes in the same way on passage from one hydroxyl-containing solvent to another. It is noteworthy that the tautomeric equilibrium constant in dichloroethane is the same as in water or alcohols. Neither the Meyer law nor the Eistert-Geiss hypothesis is applicable to "trans-fixed" ketoenols of this type.

TABLE 4. Cis-enol Content of Enolic Fraction of α -Substituted Acetoacetic Esters

Substituent R in $\text{CH}_3\text{CO}(\text{HCOOC}_2\text{H}_5)_2$ R	E	E_1	Cis-enol content in enolic fraction (%) in solvent						Reaction with ferric chloride
			67% methanol	methanol	ethanol	benzene	ether	carbon tetrachloride	
CH_3	0.319	-0.001	100	100	100	100			++
C_2H_5	0.177	0.005	46.6	74.8	83.1	89.5			++
n- C_3H_7	0.201	0.015	25.1	51.1	63.4	75.0			++
n- C_4H_9	0.156	0.033	10.6	26.9	37.9	51.5			++
n- C_7H_{15}	0.187	0.036	11.3	39.0	40.1	53.2			++
iso- C_3H_7	0.050	0.026	4.6	13.0	19.9	30.1			-
iso- C_4H_9	0.267	0.030	18.1	41.2	53.7	66.8			+
sec- C_4H_9	0.016	0.165	0.3	0.8	1.3	2.2		5.0	-
$(\text{C}_2\text{H}_5)_2\text{CH}$	0.097	0.065	3.5	10.4	16.1	25.1	37.9		+
n- $\text{C}_3\text{H}_7(\text{CH}_3)\text{CH}$	0.072	0.037	4.5	15.5	20.1	30.4	44.4	50.7	-
n- $\text{C}_4\text{H}_9(\text{CH}_3)\text{CH}$	0.037	0.046	2.0	5.9	9.4	15.5	24.7	29.9	-
n- $\text{C}_5\text{H}_{11}(\text{CH}_3)\text{CH}$	0.035	0.038	2.2	6.8	10.6	17.1			-
n- $\text{C}_8\text{H}_{17}(\text{CH}_3)\text{CH}$	0.039	0.041	1.9	7.0	11.0	17.7			-
Cyclohexyl	0.081	0.013	13.2	32.7	44.5	58.2			+
Cyclopentyl	0.008	0.13	0.2	0.5	0.8	1.4		3.30	+
$\text{C}_6\text{H}_5\text{CH}_2$	0.362	0.007	55.5	79.9	86.8	91.9			++

* ++ instantaneous coloration; + weak coloration after some time; - absence of coloration.

TABLE 5. Cis-enol Content in Enolic Fraction of α -Phenyl-acetoacetic Ester

E	E_1	Enolic content in enolic fraction (%) in solvent				
		acetic acid	chloroform	ethyl acetate	benzene	toluene
4.722	0.006	98.1	98.7	99.2	99.5	99.6

3. Cyclic acetals of malonic acid of the type of isopropylidenealkyl malonate. Here there is negligible enolization in all solvents, and we cannot speak of an influence of solvent on enolization. The Meyer law and the Eistert-Geiss hypothesis are inapplicable.

4. Open-chain ketoenols of the type of α -alkylacetoacetic esters. As in the case of type 2, no relation was observed between trans-enolization and the nature of the solvent over a wide range. Ether again slightly increases the content of enolic forms in comparison with the remaining solvents. This characteristic unites cyclic and acyclic ketoenols belonging to the class of esters of α -alkyl- β -ketocarboxylic acids into a common class for which, to a satisfactory approximation, we can assume $L' = \text{const.}$ in formula (1). For α -alkyltetronic acids and α -alkylacetoacetic esters with strong steric hindrance for which $EL = 0$, formula (1) therefore transforms into $K_T = E'L' = \text{const.}$ and there is no relation between enolization (trans) and solvent (cis-enol is substantially absent and the reaction with ferric chloride is negative).

The presence in solution of all three forms is characteristic of α -alkylacetoacetic esters with small substituents. With a high degree of probability we may say that here again trans-enolization does not depend on the solvent as is the case with α -alkyltetronic acids or α -alkylacetoacetic esters containing branched substituents; i.e. $L' = \text{const.}$ Instead of EL being zero (as previously), we now have $EL \neq 0$, and formula (1) transforms into formula (2). The plot of K_T versus L is here a straight line with a greater or smaller slope which cuts the axis of the ordinates at a height that characterizes the trans-enolization. As we see from Table 4, the content of cis-enolic forms here increases with decreasing steric hindrance due to the alkyl radicals; these substances give a pronounced color reaction with ferric chloride. Enolization of substances of this type is best expressed by formula (2).

5. Enols forming cyanoketones studied by Roussel. Here again the trans- and cis-enolic forms possess an open

TABLE 6. Properties of the Investigated α -Alkylacetoacetic Esters

Substituent R in $\text{CH}_3\text{COCH(R)COOC}_2\text{H}_5$	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	Literature data	% C		% H	
					found	calc.	found	calc.
CH_3	66–66.5° (8)	1.4200	0.9989	B. p. 75–76.5° (12 mm), n_D^{15} 1.4237 [9]	57.8, 58.0	58.3	8.4, 8.6	8.3
iso- C_4H_9	105–108 (16)	1.4300	0.9511	B. p. 104–106° (14 mm) [10]	64.7, 64.6	64.6	9.7, 9.7	9.7
n- $\text{C}_3\text{H}_7\text{CHCH}_3$	96–99 (7)	1.4350	0.9492	B. p. 226° [11]	66.0, 66.1	66.0	10.1, 10.2	10.1
$\text{C}_2\text{H}_5\text{CHCH}_3$	100 (9)	1.4375	0.9568	—	66.2, 66.1	66.0	10.1, 10.1	10.1
n- $\text{C}_4\text{H}_9\text{CHCH}_3$	118–121 (10)	1.4370	0.9433	B. p. 130–132° (17 mm) [12]	67.2, 67.2	67.2	10.4, 10.3	10.3
n- $\text{C}_5\text{H}_{11}\text{CHCH}_3$	123–124 (8)	1.4388	0.9331	B. p. 250–260° [13]	68.7, 68.6	68.5	10.8, 10.4	10.6
sec- C_4H_9	68 (3)	1.4350	0.9584	B. p. 102–104° (15 mm) [14]	64.5, 64.6	64.5	9.8, 9.8	9.7
n- $\text{C}_6\text{H}_{13}\text{CHCH}_3$	114–116 (2)	1.4397	0.9254	B. p. 280–282° [15]	69.6, 69.7	69.4	11.0, 11.1	10.8
n- C_7H_{15}	122–124 (3)	1.4365	0.9291	B. p. 141.6° (10 mm) n_D^{15} 1.4376, d_4^{15} 0.9327 [16]	68.1, 68.2	68.5	10.5, 10.5	10.6
Cyclopentyl	115 (7)	1.4570	1.0155	B. p. 118–120° (12 mm) n_D^{20} 1.4646 [17]	66.7, 67.0	66.6	9.1, 9.3	9.2
Cyclohexyl*	95–96 (3)	1.4618	1.0386	B. p. 146–148° (12 mm) [18]	67.9, 67.6	67.9	9.3, 9.3	9.5
C_6H_5 **	113–115 (2.5)	1.5170	1.0855	B. p. 130–134° (5 mm) [19]	69.9, 70.0	69.9	6.8, 6.9	6.8
$\text{C}_6\text{H}_5\text{CH}_2$	110.5–112 (2)	1.5056	1.0636	B. p. 164–165° (12 mm) [20]	70.6, 70.4	70.9	7.3, 7.3	7.3

* Prepared from ethyl acetoacetate, cyclohexanol, and boron fluoride.

** Prepared via α -phenyl- α -acetylacetonitrile.

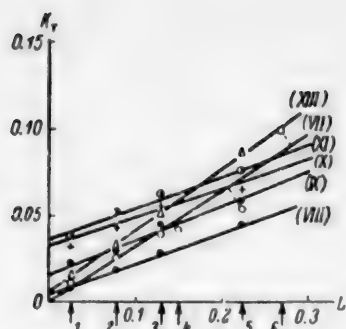


Fig. 5. Tautomeric equilibrium constant (K_T) as a function of the solvent (constant L) for α -substituted acetoacetic esters containing unbranched substituents. $\text{CH}_3\text{COCHRCOOC}_2\text{H}_5$: (VII) $R = \text{CH}_3$, (VIII) $R = \text{C}_2\text{H}_5$; (IX) $R = \text{H} - \text{C}_3\text{H}_7$, (X) $R = \text{H} - \text{C}_4\text{H}_9$, (XI) $R = \text{H} - \text{C}_7\text{H}_{15}$, (XIII) $R = \text{C}_6\text{H}_5\text{CH}_2$. Solvents: 1) 67% CH_3OH , 2) CH_3OH , 3) $\text{C}_2\text{H}_5\text{OH}$, 4) $\text{CH}_3\text{COOC}_2\text{H}_5$, 5) C_6H_6 , 6) $\text{C}_6\text{H}_5\text{CH}_3$.

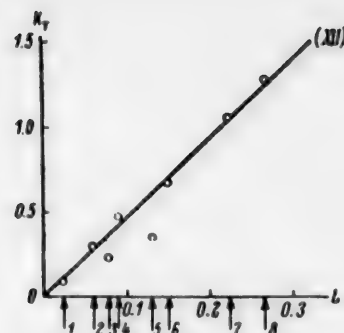


Fig. 6. Tautomeric equilibrium constant (K_T) as a function of the solvent (constant L) for α -phenylacetoacetic ester. Solvents: 1) 67% CH_3OH , 2) CH_3COOH , 3) CH_3OH , 4) CHCl_3 , 5) $\text{C}_2\text{H}_5\text{OH}$, 6) $\text{CH}_3\text{COOC}_2\text{H}_5$, 7) C_6H_6 , 8) $\text{C}_6\text{H}_5\text{CH}_3$.

The value of K_T passes through a maximum with increasing degree of cis-enolizing ability of the solvent (Meyer's constant L). These curves change into straight lines when L' (formula 1) is used instead of L , i.e., with change of the reference substance. If any one of the cyanoketones is taken as the reference substance, good linear plots are ob-

hydroxyl group. The relation between enolization and solvent is here a complex one as illustrated by Fig. 8 where K_T is plotted against L .

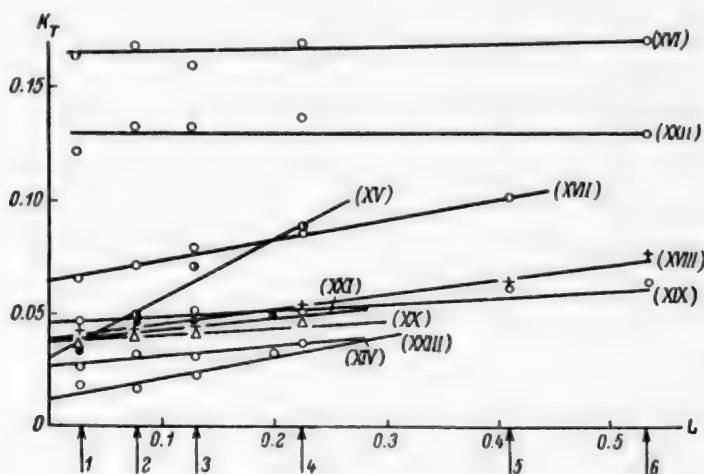


Fig. 7. Tautomeric equilibrium constant (K_T) as a function of the solvent (constant L) for α -substituted acetoacetic esters containing branched substituents. $\text{CH}_3\text{CHRCOOC}_2\text{H}_5$: (XIV) $R = \text{iso-C}_3\text{H}_7$; (XV) $R = \text{iso-C}_4\text{H}_9$; (XVI) $R = \text{sec-C}_4\text{H}_9$; (XVII) $R = 3\text{-pentyl}$; (XVIII) $R = 2\text{-pentyl}$; (XIX) $R = 2\text{-hexyl}$; (XX) $R = 2\text{-heptyl}$; (XXI) $R = 2\text{-octyl}$; (XXII) $R = \text{cyclopentyl}$; (XXIII) $R = \text{cyclohexyl}$. Solvents: 67% CH_3OH ; 2) CH_3OH , 3) $\text{C}_2\text{H}_5\text{OH}$, 4) C_6H_6 , 5) ether, 6) CCl_4 .

tained and the straight lines pass through the origin of the coordinates (Fig. 9). Since enolization with formation of a chelated enol is here impossible, $E = 0$ and formula (1) transforms into a formula similar to Meyer's formula, $K_T = E'L'$, but differing from it in the choice of reference substance. In this case again, the relatively high enolizing

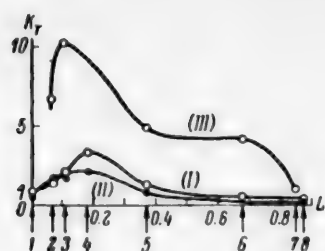


Fig. 8. Tautomeric equilibrium constant (K_T) of cyanoketones as a function of the solvent (constant L ; reference substance ethyl acetoacetate). I) α -cyano-desoxybenzoin; II) α -(2-furoyl) phenylacetone; III) α -(2-furoyl)-3,4-dichlorophenylacetone. Solvents: 1) water, 2) methanol, 3) ethanol, 4) amyl alcohol, 5) ether, 6) mixture (1 : 1) of ether and hexane, 7) mixture (9 : 1) of hexane and ether, 8) hexane.

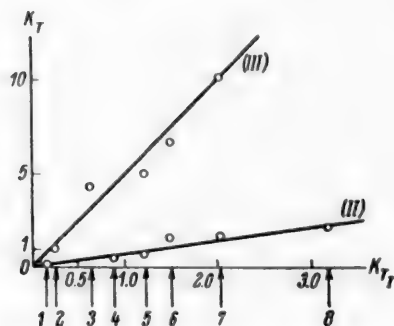


Fig. 9. Relation between tautomeric equilibrium constant (K_T) of cyanoketones and solvent [constant L' ; reference substance α -cyanodesoxybenzoin (1)]. See Fig. 8 for details.

ability of ether is evidently associated with formation of hydrogen bonds with the open hydroxyl group of the enolic form. Consequently the Meyer law and the Eistert-Geiss hypothesis are not applicable here. Formula $K_T = E'L'$ is applicable with a reliable choice of reference substance.

The types of ketoenols here discussed certainly do not exhaust all the possibilities of the influence of solvents on trans-enolization. However these examples will have indicated the diversity of types of these influences. The Eistert-Geiss hypothesis is only valid for some special types (e.g. dimedon type).

We see from the foregoing discussion that formula (1) has a universal value, and the practical success of its application depends on the correctness of choice of the reference substances for L and L' . Formula (2) has only limited value and is applicable only to systems for which $L' = \text{const}$ is characteristic.

EXPERIMENTAL

α -Substituted acetoacetic esters were prepared by alkylation of sodium ethyl acetoacetate with the appropriate alkyl halides. The properties of the investigated substances are set forth in Table 6. Bromometric titration of 1% solutions was performed by the method of Hess and Krehbiel [21] with alcoholic bromine solution. The infrared spectra were obtained with a two-beam IKS-14 spectrophotometer. Specimens for observation on the crystalline compounds were prepared by pelleting with potassium bromide. The ultraviolet spectra were obtained with a SFD-1 apparatus.

SUMMARY

It was shown that the influence of the solvent on trans-enolization of ketoenols depends appreciably on the nature of the ketoenol. The keto-enol equilibrium of α -alkyltetronic acids, isopropylidenealkyl malonates, and α -alkylacetoacetic esters was investigated with the help of the ultraviolet and infrared spectra. In the last case use was also made of bromometric titration. The limited applicability of the Meyer law and of the Eistert-Geiss hypothesis to trans-enolization was established. The general character of the relation $K = EL + E'L'$ and special cases of its application were shown.

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ASSOCIATION AND DEPENDENCE ON CONCENTRATION OF PROPERTIES OF BINARY MIXTURES OF ORGANIC COMPOUNDS

III. MIXTURES OF ISOPERIODIC COMPOUNDS*

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Under the same external conditions (pressure p and temperature T), the value and sign of $\Delta y_{1,2 \dots r} = y_{1,2 \dots r} - \sum_{i=1}^r y_i^0$, the deviations from additivity of any property y (y^0 is the property of the pure substance) of a mixture, under the condition that chemical interaction is absent, are determined in the final analysis by the differences in the properties of the molecules of the components of the mixture — their mass (m), size (v_M), shape (s), polarizability (α), and dipole moment (μ) [2]. It is specifically for this reason that the validity of the proposed theories is usually checked on the data for such mixtures where the molecules of the components differ only in some of the above indicated properties, and specifically only in size [3], shape [4], or only in cohesive forces [5].** In connection with this, considerable interest is also possessed by a mixture of compounds, belonging to the same isoperiodic series. As a rule, the molecules in compounds of this type differ noticeably only in the dipole moment (Table 1), and also in [6]) and also in the tendency shown by some of them to form complexes via hydrogen bonds. The structure (interaction parameters ϵ^* and r^* , number of neighbors z) of the pure components in mixtures of this type should hypothetically not undergo any important changes [7], and the peculiarities of their behavior should make it possible to disclose the effect on the properties of mixtures like the association of molecules, as well as the dipole-dipole interaction between unlike molecules [2].

TABLE 1. Properties of Molecules of Compounds
of the Same Isoperiodic Series

Compound	$m \cdot 10^{22}$ (r)	$v_M \cdot 10^{24}$ (cm ³) [10]	$\alpha \cdot 10^{24}$ (cm ³)	$\mu \cdot 10^{18}$
C ₂ H ₅ NHC ₂ H ₅	12.14	80.52	9.51	0.92
C ₂ H ₅ OC ₂ H ₅	12.33	77.47	8.10	1.14
CH ₃ CH ₂ CH ₂ OH	12.33	77.47	8.10	1.66
HCOOCH ₂ CH ₃	12.30	67.32	7.06	1.92
CH ₃ COCH ₂ CH ₃	11.97	72.40	8.19	2.76
CH ₃ CH ₂ NO ₂	12.47	68.32	6.70	3.2

In Table 2-4 we have given the results of measuring the density ($\rho_{1,2}$), viscosity coefficients ($\eta_{1,2}$) and dielectric permeability ($\epsilon_{1,2}$) of binary mixtures composed of members of the same series of isoperiodic compounds with each other in the concentration range from 0.0 to 1.0 mole fraction of (X). The technique and accuracy of the measurements, as well as the purification of the compounds, were given earlier [1, 8]. Since the η^0 and ρ^0 of members of the same series of isoperiodic compounds change linearly with μ , while ϵ^0 changes linearly with μ^2 [9], it could be expected, under the condition of a constancy in the structure, that simple rules of the same type would also hold

* See [1] for Communications I and II.

** However, here it is started [3-5] with the differences in the molar volume V (and not in v_M) or in the boiling points (and not in α and μ) of the pure components, which fails to reflect by far the actual differences in the properties of the corresponding molecules.

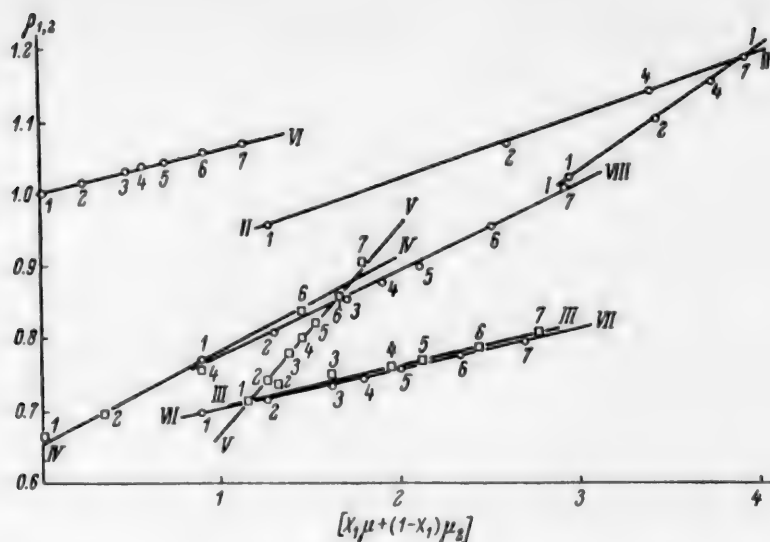


Fig. 1. Dependence of the density $\rho_{1,2}^{25/4}$ of binary mixtures on the dipole moment. I) $C_6H_5NO_2 + C_6H_5COCH_3$, II) $C_6H_5NO_2 + C_6H_5OC_2H_5$, III) $CH_3COC_2H_5 + C_2H_5OC_2H_5$, IV) $CH_3COOC_2H_5 + n-C_6H_{14}$, V) $HCOOC_2H_5 + C_2H_5OC_2H_5$, VI) $C_6H_5OC_2H_5 + C_6H_5CH_2C_6H_5$ [11], VII) $CH_3COC_2H_5 + C_2H_5NHC_2H_5$, VIII) $CH_3COCH_2COOC_2H_5 + C_4H_9OC_4H_9-n$. Values of X_1 : 1) 0.0; 2) 0.2; 3) 0.4; 4) 0.5; 5) 0.6; 6) 0.8; 7) 1.0.

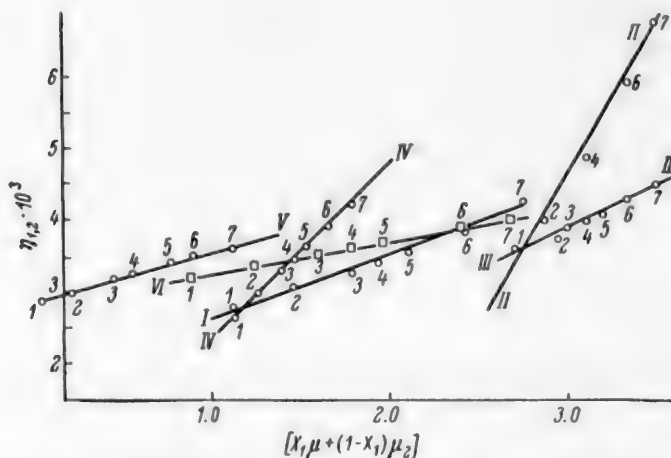


Fig. 2. Dependence of the viscosity $\eta_{1,2} \cdot 10^3$ (25°) of binary mixtures on the dipole moment. I) $CH_3COC_2H_5 + C_2H_5OC_2H_5$, II) $CH_3NO_2 + CH_3COCH_3$, III) $C_2H_5CN + CH_3COCH_3$, IV) $HCOOC_2H_5 + C_2H_5OC_2H_5$, V) $C_6H_5OC_2H_5 + C_6H_5CH_2C_6H_5$, VI) $C_2H_5COCH_3 + C_2H_5NHC_2H_5$. Values of X_1 : 1) 0.0; 2) 0.2; 3) 0.4; 4) 0.5; 5) 0.6; 6) 0.8; 7) 1.0.

for these properties of their mixtures. Actually, as follows from Figs. 1 and 2 (and also from Fig. 6 in [8]), the values $\rho_{1,2}$ and $\eta_{1,2}$ of the studied mixtures of compounds, not containing groups inclined to form hydrogen bonds, change proportionally to $\mu_{1,2} = X_1\mu_1^0 + (1-X_1)\mu_2^0$ over the entire concentration range, while the term $\epsilon_{1,2}-1$ changes proportionally to $\mu_{1,2}^2 = [X_1\mu_1^0 + (1-X_1)\mu_2^0]^2$ (Fig. 3). In this connection the deviations from a strict linearity with $\mu_{1,2}$ or $\mu_{1,2}^2$ are evidently caused mainly by those small differences, existing also for isoperiodic compounds, in the properties of the molecules of the components other than μ . The validity of this follows from the increase in these devia-

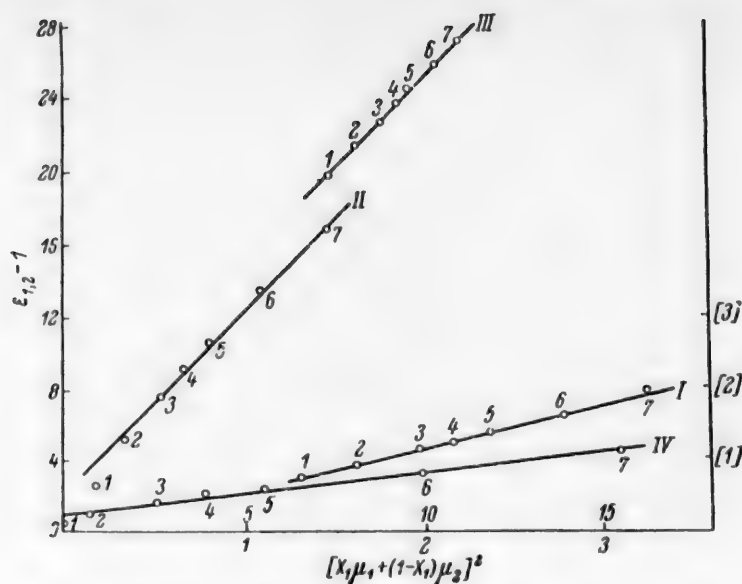


Fig. 3. Dependence of the dielectric permeability ($\epsilon_{1,2}-1$) (25°) of binary mixtures on the dipole moment. I) $\text{HCOOC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OC}_2\text{H}_5$, II) $\text{CH}_3\text{COC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$, III) $\text{C}_2\text{H}_5\text{CN} + \text{CH}_3\text{COCH}_3$, IV) $\text{CH}_3\text{COC}_3\text{H}_7\text{-n} + \text{n-C}_7\text{H}_{16}$. Values of X_1 : 1) 0.0; 2) 0.2; 3) 0.4; 4) 0.5; 5) 0.6; 6) 0.8; 7) 1.0.

tions specifically for those mixtures of components that differ more noticeably in the shape and size of the molecules (nitromethane and acetone, esters and normal hydrocarbons, acetoacetic ester and dibutyl ether).*

Mixtures of isoperiodic compounds with one component, the molecules of which contain carboxyl, hydroxyl or oxime groups, i.e., associated in the pure state because of hydrogen bonding between the molecules, fail completely in obeying the indicated dependence on $\mu_{1,2}$ or $\mu_{1,2}^2$. In this case $\rho_{1,2}$ and $\eta_{1,2}$, as a rule, decrease with increase in $\mu_{1,2}$. Evidently, effects are present in mixtures containing compounds of this type which to a large measure or completely compensate the effect of dipole-dipole interaction.

As a rule, comparatively small absolute values of $\Delta\rho_{1,2}$, $\Delta\eta_{1,2}$ and $\Delta\epsilon_{1,2}$ are observed for mixtures of normal (devoid of OH groups) isoperiodic compounds (Figs. 4-6, Table 5, where the values of the corresponding $\Delta y_{1,2}/y_{1,2}$ - the relative deviations from additivity at $X_1 = X_2 = 0.5$ - are also given). The closeness of the discussed type of mixtures (propionitrile-acetone [5], o- and p-xylenes [12], etc.) to the "ideal" mixture was also established when their thermodynamic properties were studied. The increase in the values of $\Delta y_{1,2}/y_{1,2}$ for mixtures of nitromethane and acetone, esters and hydrocarbons, and acetoacetic ester and dibutyl ether, can be explained only by the fact that the indicated deviations from additive values are due more to the difference in the other properties of the molecules of the components than to the difference in their μ values, and primarily they are due to the difference in the size and shape. As evidence of this is the fact that for the discussed mixtures a proportionality of the terms $\Delta y_{1,2}/y_{1,2}$ and $y_1^0 - y_2^0$ is absent, as is also a reversal of the sign of $\Delta v_{1,2}/v_{1,2}$ when going from mixtures of benzene with aromatic isoperiodic compounds to its mixtures with aliphatic isoperiodic compounds [1, 8], i.e., to mixtures with another kind of difference - mainly in the shape, size and polarizability of the molecules of the components. Obviously, for mixtures, the molecules of whose components differ strictly only in the dipole moment, the values of $\Delta y_{1,2}$, especially $\rho_{1,2}$ and $\eta_{1,2}$, should approach zero, and not be proportional, as was postulated in the case of $\Delta v_{1,2}$, to the values of $\mu_{1,2}$, or they are a function of μ^2 [2, 13]. The explanation for this must be sought in the fact that a reduction in the order and dipole-dipole interaction between the molecules of the more polar component on mixing is to a large degree compensated by a concurrent increase in the order of the distribution and forces of dipole-dipole interaction between molecules of different components or of the inductive interaction between the molecules of polar and nonpolar components [2].

* In the case of mixtures with a small difference in the μ values of the molecules of the components a superimposition of the effect of the differences in their other properties can even be cited for certain macrophysical properties (for example, for the $\eta_{1,2}$ of the mixture diethylamine-diethyl ether) and lead to a complete noncompliance with the indicated rules.

TABLE 2. Density ($\rho_{1,2}$) of Binary Mixtures

Mixture No.	Components		Temperature	Mole fraction of component 1 (X_1)						
	1	2		0.0	0.2	0.4	0.5	0.6	0.8	1.0
1	$\text{CH}_3\text{COC}_2\text{H}_5$	$(\text{C}_2\text{H}_5)_2\text{O}$	20°	0.7136	0.7316	0.7498	0.7589	0.7682	0.7865	0.8051
2	$(\text{C}_2\text{H}_5)_2\text{NH}$	$(\text{C}_2\text{H}_5)_2\text{O}$	25	0.7083	0.7063	0.7046	0.7038	0.7028	0.7014	0.7003
3	$\text{n-COOCC}_2\text{H}_5$	$(\text{C}_2\text{H}_5)_2\text{O}$	25	0.7083	0.7420	0.7783	0.7981	0.8178	0.8605	0.9073
4	$\text{n-C}_4\text{H}_9\text{OH}$	$(\text{C}_2\text{H}_5)_2\text{O}$	25	0.7083	0.7309	0.7514	0.7613	0.7708	0.7893	0.8063
5	$\text{n-C}_4\text{H}_9\text{OH}$	$(\text{C}_2\text{H}_5)_2\text{NH}$	25	0.7007	0.7284	0.7540	0.7623	0.7759	0.7932	0.8063
6	HCOOC_2H_5	$(\text{C}_2\text{H}_5)_2\text{NH}$	25	0.6996	0.7403	0.7849	0.8085	0.8330	0.8708	0.9094
7	$\text{CH}_3\text{COC}_2\text{H}_5$	$(\text{C}_2\text{H}_5)_2\text{NH}$	25	0.6996	0.7179	0.7366	0.7466	0.7566	0.7777	0.8004
8	$\text{C}_2\text{H}_5\text{CN}$	CH_3COCH_3	20	0.7898	0.7884	0.7872	0.7803	0.7855	0.7843	0.7829
9	CH_3NO_2	CH_3COCH_3	20	0.7898	0.8464	—	0.9405	—	1.0514	1.1373
10	$\text{CH}_3\text{COOC}_2\text{H}_5$	$\text{n-C}_3\text{H}_7$	20	0.6607	0.6947	—	0.7579	—	0.8352	0.8987
11	$\text{CH}_3\text{COOC}_3\text{H}_7$	$\text{n-C}_3\text{H}_7$	25	0.6797	0.7102	0.7452	0.7647	0.7849	0.8293	0.8802
12	$\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$	$(\text{n-C}_4\text{H}_9)_2\text{O}$	25	0.7734	0.8121	0.8543	0.8777	0.9024	0.9568	1.0167
13	$\text{n-C}_3\text{H}_7\text{OH}$	CH_3COCH_3	20	0.7898	0.7936	0.7973	0.7988	0.8005	0.8038	0.8065
14	$\text{CH}_2=\text{CHCH}_2\text{OH}$	CH_3COCH_3	25	0.7854	0.8010	0.8154	0.8233	0.8301	0.8434	0.8529
15	$\text{CH}_3\text{CH}=\text{NOH}$	CH_3COCH_3	25	0.7842	0.8207	0.8567	0.8743	0.8931	—	0.9666
16	$\text{HOCH}_2\text{CH}_2\text{OH}$	CH_3COCH_3	25	0.7898	0.8490	0.9105	0.9428	0.9754	1.0438	1.1128
17	CH_3COOH	CH_3COCH_3	25	0.7842	0.8327	0.8826	0.9080	0.9340	0.9889	1.0452
18	CH_3COOH	CH_3NO_2	25	1.1311	1.1137	1.0965	1.0883	1.0801	1.0637	1.0469
19	CH_3COOH	$\text{n-C}_3\text{H}_7\text{OH}$	25	0.8032	0.8431	0.8861	0.9109	0.9359	0.9895	1.0479
20	$\text{C}_2\text{H}_5\text{CN}$	$\text{n-C}_3\text{H}_7\text{OH}$	20	0.8065	0.8021	0.7970	0.7947	0.7918	0.7872	0.7829
21	CH_3NO_2	$\text{n-C}_3\text{H}_7\text{OH}$	25	0.8032	0.8511	0.9060	0.9366	0.9693	1.0425	1.1311

TABLE 3. Viscosity ($\eta_{1,2} \cdot 10^3$) of Binary Mixtures

Mixture No.	Components		Temperature	Mole fraction of component 1 (X_1)							
	1	2		0.0	0.2	0.4	0.5	0.6	0.8	1.0	
1	$\text{CH}_3\text{COC}_2\text{H}_5$	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	20	2.79	3.08	3.25	3.40	3.54	3.86	4.24	
2	$\text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	25	2.68	2.75	2.85	2.91	2.96	3.13	3.26	
3	HCOOC_2H_5	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	25	2.68	2.99	3.30	3.45	3.61	3.92	4.23	
4	$n\text{-C}_4\text{H}_9\text{OH}$	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	25	2.68	3.32	4.53	5.56	6.92	12.17	24.42	
5	$n\text{-C}_4\text{H}_9\text{OH}$	$\text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$	25	3.26	4.46	6.68	8.38	10.61	16.71	24.42	
6	HCOOC_2H_5	$\text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$	25	3.20	3.61	3.89	4.44	4.68	4.65	4.21	
7	$\text{CH}_3\text{COC}_2\text{H}_5$	$\text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$	25	3.20	3.35	3.49	3.57	3.65	3.82	4.04	
8	$\text{C}_2\text{H}_5\text{CN}$	CH_3COCH_3	20	3.55	3.73	3.90	4.00	4.06	4.28	4.49	
9	CH_3NO_2	CH_3COCH_3	20	3.55	4.02	—	4.85	—	5.89	6.77	
10	$\text{CH}_3\text{COOC}_2\text{H}_5$	$n\text{-C}_6\text{H}_{14}$	20	3.33	3.40	—	3.70	—	4.22	4.79	
11	$\text{CH}_3\text{COOC}_3\text{H}_7\text{-}n$	$n\text{-C}_7\text{H}_{18}$	25	3.99	4.06	4.27	4.41	4.58	4.98	5.58	
12	$\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$	$n\text{-C}_4\text{H}_9\text{OC}_4\text{H}_9\text{-}n$	25	6.44	7.16	8.23	8.88	9.58	11.53	14.09	
13	$n\text{-C}_3\text{H}_7\text{OH}$	CH_3COCH_3	20	3.55	4.12	5.17	5.99	7.17	11.39	22.15	
14	$\text{CH}_2=\text{CHCH}_2\text{OH}$	CH_3COCH_3	25	3.43	3.98	4.71	5.33	6.10	8.38	12.22	
15	$\text{CH}_3\text{CH}=\text{NOH}$	CH_3COCH_3	25	3.41	4.33	5.85	7.09	8.67	—	23.59	
16	$\text{HOCH}_2\text{CH}_2\text{OH}$	CH_3COCH_3	20	3.39	5.51	11.25	16.59	26.79	71.69	207.84	
17	CH_3COOH	CH_3COCH_3	25	3.41	4.26	5.40	6.14	7.02	9.12	12.33	
18	CH_3COOH	CH_3NO_2	25	6.37	6.78	7.47	7.94	8.55	10.04	12.43	
19	CH_3COOH	$n\text{-C}_3\text{H}_7\text{OH}$	25	19.31	17.27	16.48	16.27	15.74	14.58	12.75	
20	$\text{C}_2\text{H}_5\text{CN}$	$n\text{-C}_3\text{H}_7\text{OH}$	20	22.15	12.31	8.20	7.00	6.12	5.00	4.49	
21	CH_3NO_2	$n\text{-C}_3\text{H}_7\text{OH}$	25	19.31	12.22	9.21	8.04	7.24	6.26	6.37	

TABLE 4. Dielectric Permeability ($\epsilon_{1,2}$) of Binary Mixtures

Mixture No.	Components		Temperature	Mole fraction of component 1 (X_1)						
	1	2		0.0	0.2	0.4	0.5	0.6	0.8	1.0
2	$C_2H_5NHC_2H_5$	$C_2H_5OC_2H_5$	25°	4.00	3.90	3.80	3.75	3.73	3.70	3.65
3	$HCOOC_2H_5$	$C_2H_5OC_2H_5$	25	4.10	4.70	5.55	5.95	6.45	7.40	8.70
4	$n-C_4H_9OH$	$C_2H_5OC_2H_5$	25	4.10	5.40	7.40	8.70	10.00	13.40	17.25
5	$n-C_4H_9OH$	$C_2H_5NHC_2H_5$	25	3.65	5.85	8.50	9.90	11.35	14.25	17.25
6	$HCOOC_2H_5$	$C_2H_5NHC_2H_5$	25	3.80	6.65	—	—	—	—	8.55
7	$CH_3COC_2H_5$	$C_2H_5NHC_2H_5$	25	3.65	6.10	8.65	10.10	11.50	14.45	17.80
8	C_2H_5CN	CH_3COCH_3	20	20.75	22.40	23.85	24.70	25.50	26.80	27.90
11	$CH_3COOC_3H_7-n$	$n-C_7H_{16}$	25	1.50	2.10	2.75	3.13	3.68	4.40	5.45
12	$CH_3COCH_2COOC_2H_5$	$n-C_4H_9OC_4H_9$	25	3.15	4.65	6.65	7.70	9.15	12.10	15.85
13	$n-C_3H_7OH$	CH_3COCH_3	20	20.7	19.5	18.9	18.8	18.8	19.2	20.35
14	$CH_3=CHCH_2OH$	CH_3COCH_3	25	20.35	20.55	21.10	21.0	21.3	22.1	23.1
15	$CH_3CH=NOH$	CH_3COCH_3	25	20.35	17.55	14.0	12.65	11.05	—	4.70
16	$HOCH_2CH_2OH$	CH_3COCH_3	20	20.70	24.3	27.1	29.0	30.8	35.3	40.8
19	CH_3COOH	$n-C_3H_7OH$	25	20.35	18.25	16.50	15.85	14.75	12.35	8.85
20	C_2H_5CN	$n-C_3H_7OH$	20	20.70	21.80	23.20	24.10	24.70	26.46	27.90
21	CH_3NO_2	$n-C_3H_7OH$	25	20.35	21.00	22.60	23.75	25.50	29.30	34.85

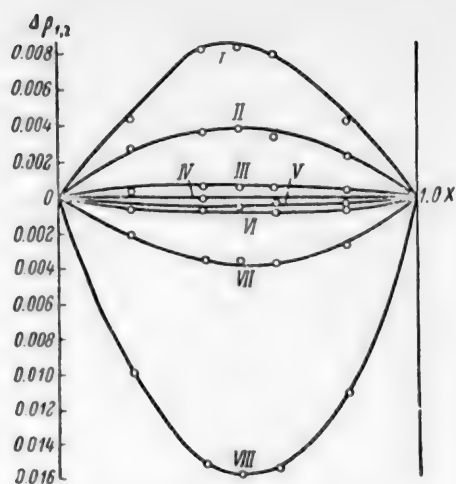


Fig. 4. Change in $\Delta\rho_{1,2}$ of binary mixtures with the concentration at 20°. I) $\text{CH}_2\text{OHCH}_2\text{OH} + \text{CH}_3\text{COCH}_3$, II) $n\text{-C}_4\text{H}_9\text{OH} + \text{C}_2\text{H}_5\text{OC}_2\text{H}_5$ (25°), III) $n\text{-C}_3\text{H}_7\text{OH} + \text{CH}_3\text{COCH}_3$, IV) $\text{C}_2\text{H}_5\text{CN} + \text{CH}_3\text{COCH}_3$, V) $\text{CH}_3\text{COC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OC}_2\text{H}_5$, VI) $\text{C}_2\text{H}_5\text{NHC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OC}_2\text{H}_5$, VII) $\text{CH}_3\text{COC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{-NHC}_2\text{H}_5$ (25°), VIII) $\text{CH}_3\text{COOC}_3\text{H}_7\text{-n} + \text{C}_7\text{H}_{16}$ (25°).

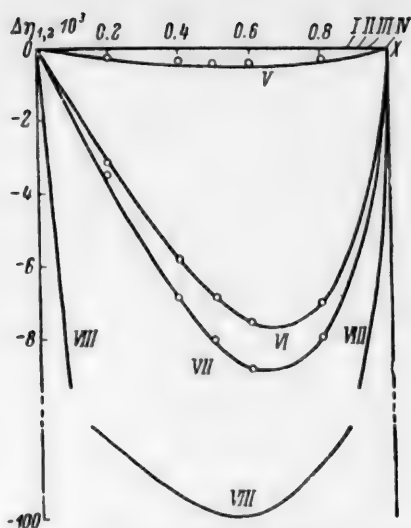


Fig. 5. Change in $\Delta\eta_{1,2}$ (25°) of binary mixtures with the concentration. I) $\text{CH}_3\text{COCH}_3 + \text{C}_2\text{H}_5\text{CN}$ (20°), II) $\text{CH}_3\text{COC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OC}_2\text{H}_5$ (20°), III) $\text{CH}_3\text{COC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$, IV) $\text{C}_2\text{H}_5\text{OC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{-NHC}_2\text{H}_5$, V) $\text{CH}_3\text{COOC}_3\text{H}_7\text{-n} + n\text{-C}_7\text{H}_{16}$, VI) $\text{CH}_3\text{COCH}_3 + n\text{-C}_3\text{H}_7\text{OH}$, VII) $\text{C}_2\text{H}_5\text{OC}_2\text{H}_5 + n\text{-C}_4\text{H}_9\text{OH}$, VIII) $\text{CH}_3\text{COCH}_3 + \text{CH}_2\text{OHCH}_2\text{OH}$.

As a rule, there is no significant difference in the absolute value of $\Delta\rho_{1,2}/\rho_{1,2}$ and $\Delta\epsilon_{1,2}/\epsilon_{1,2}$ between mixtures with one component associated in the pure liquid (alcohols, acid, oxime) and mixtures of nonassociated isoperiodic compounds. For the first when compared with the second there is observed (Table 5): a) a sharp increase in the values of $\Delta\eta_{1,2}/\eta_{1,2}$ (especially in the case of mixtures containing alcohols or the oxime) with retention of the same sign, reaching several hundred percent for the mixture containing glycol; and b) a change, as a rule, in the sign of $\Delta\rho_{1,2}/\rho_{1,2}$ from negative to positive (Fig. 4). Here mention should be made of the great sensitivity of the examined mixtures to a difference in the shape, size and polarizability of the molecules of the components, which is evidenced by the opposite sign of $\Delta v_{1,2}/v_{1,2}$ for mixtures of acetone with isopropyl alcohol when compared with its mixture with *n*-propyl alcohol, and of benzene with *n*-butyl alcohol when compared with its mixture with benzyl alcohol, or by the reversal of sign for $\Delta v_{1,2}$ for the mixture acetonitrile-ethanol at $\Delta v_{1,2} \approx 0$ or the mixture propionitrile-*n*-propyl alcohol [1, 5]. The peculiarities of the discussed mixtures are usually associated with a destruction of the complexes of the molecules of the associated compound when it is mixed with a nonpolar or a polar component. In this case, with a complete destruction of the complexes, a coinciding of the signs and a closeness of the absolute values of the different $\Delta y_{1,2}$ of these mixtures to those for the difference $y_1^0 - y_2^0$ of the pure alcohol (or acid) and the corresponding esters - members of the same isoperiodic series - could be expected. Thus, for the mixture containing *n*-butyl alcohol it could be expected, at $X_1 = X_2 = 0.5$, that $\Delta\rho_{1,2} \approx -0.04$, $\Delta\eta_{1,2} \cdot 10^3 \approx -11.0$, and $\Delta\epsilon_{1,2} \approx -6.5$. For mixtures containing *n*-propyl alcohol it could be expected that the corresponding values would be ~ -0.04 , ~ -10.0 , and ~ -6.0 . The positive sign of $\Delta\rho_{1,2}$ (also observed for certain mixtures of benzene with alcohols [1]) and,

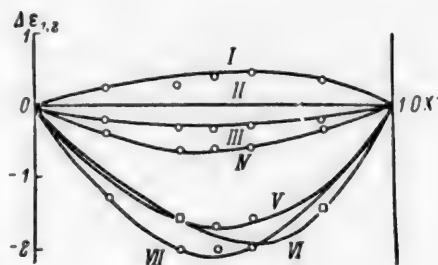


Fig. 6. Change in $\Delta\epsilon_{1,2}$ (25°) of binary mixtures with the concentration. I) $\text{CH}_3\text{COCH}_3 + \text{C}_2\text{H}_5\text{CN}$, II) $\text{C}_2\text{H}_5\text{OC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$, III) $\text{CH}_3\text{COOC}_3\text{H}_7\text{-n} + n\text{-C}_7\text{H}_{16}$, IV) $\text{CH}_3\text{COC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$, V) $\text{CH}_3\text{COCH}_3 + n\text{-C}_3\text{H}_7\text{OH}$, VI) $\text{CH}_3\text{COCH}_3 + \text{HOCH}_2\text{CH}_2\text{OH}$, VII) $\text{C}_2\text{H}_5\text{OC}_2\text{H}_5 + n\text{-C}_4\text{H}_9\text{OH}$.

TABLE 5. Values of $\Delta y_{1,2}$ and $\Delta y_{1,2}/y_{1,2}$ for Mixtures of Isoperiodic Compounds at $X_1 = X_2 = 0.5$

Components		$y = p$			$y = \gamma$			$y = \epsilon$		
1	2	$p_1 - p_2$	$\Delta p_{1,2}$	$\frac{\Delta p_{1,2}}{p_{1,2}} \cdot 100$	$\gamma_1 - \gamma_2$	$\Delta \gamma_{1,2}$	$\frac{\Delta \gamma_{1,2}}{\gamma_{1,2}} \cdot 100$	$\epsilon_1 - \epsilon_2$	$\Delta \epsilon_{1,2}$	$\frac{\Delta \epsilon_{1,2}}{\epsilon_{1,2}} \cdot 100$
$\text{CH}_3\text{COC}_2\text{H}_5$	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	+0.073	-0.0004	-0.05	+1.07	-0.11	-3.2	-	-	-
$\text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	-0.008	-0.0005	-0.07	-0.58	-0.06	-2.1	+0.3	-0.07	-1.8
CH_3COCH_3	$\text{C}_2\text{H}_5\text{CN}$	+0.007	0	0	-0.97	-0.02	0.5	-7.15	+0.38	+1.5
$\text{CH}_3\text{COC}_2\text{H}_5$	$\text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$	+0.101	-0.0034	-0.45	+0.84	-0.05	-1.4	+14.15	-0.62	-6.0
$\text{CH}_3\text{COC}_2\text{H}_5$ [8]	$\text{C}_6\text{H}_5\text{COCH}_3$	+0.175	-0.0060	-0.50	+1.62	-0.27	-1.6	-	-	-
HCOOC_2H_5	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	+0.199	-0.0097	-1.2	+1.55	-0.16	+4.6	+4.6	-0.45	-7.6
CH_3NO_2	CH_3COCH_3	+0.340	-0.0239	-2.5	+3.16	-0.34	-7.0	-	-	-
$\text{CH}_3\text{COC}_2\text{H}_5$	n.- C_6H_{14}	+0.238	-0.0218	-2.8	+1.46	-0.36	-9.7	-	-	-
$\text{CH}_3\text{COC}_3\text{H}_7$	n.- C_7H_{16}	+0.201	-0.0153	-2.0	+1.59	-0.38	-8.6	+3.9	-0.35	-11.2
$\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$	(n.- $\text{C}_4\text{H}_9\text{O}$)	+0.243	-0.173	-1.9	+7.65	-1.43	-16.3	+12.7	-1.80	-23.0
CH_3COCH_3	CH_3COOH	-0.0261	-0.0067	-0.74	-7.92	-1.23	-20.0	-	-	-
CH_3NO_2	CH_3COOH	+0.085	-0.0007	-0.07	+6.06	-1.46	-18.4	-	-	-
CH_3NO_2	n.- $\text{C}_3\text{H}_7\text{OH}$	+0.328	-0.0306	-3.2	-12.94	-4.80	-59.9	+14.5	-3.85	-16.2
CH_3COCH_3	n.- $\text{C}_3\text{H}_7\text{OH}$	-0.017	+0.0007	+0.01	-18.60	-6.86	-114.5	+0.3	-1.7	-9.0
CH_3COCH_3	$\text{CH}_2=\text{CHCH}_2\text{OH}$	-0.067	+0.0042	+0.5	-8.79	-2.49	-46.7	-2.4	-0.9	-4.2
CH_3COCH_3	$\text{CH}_3\text{CH}=\text{NOH}$	-0.182	-0.0006	-0.07	-20.18	-6.41	-90.3	+16.2	-0.15	-1.1
CH_3COCH_3	$\text{HOCH}_2\text{CH}_2\text{OH}$	-0.323	+0.0085	+0.9	-202.3	-89.1	-536.9	-20.1	-1.75	-6.0
$\text{C}_2\text{H}_5\text{CN}$	n.- $\text{C}_3\text{H}_7\text{OH}$	-0.024	0	0	-17.66	-6.32	-90.2	+7.2	-0.20	-0.83
$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	n.- $\text{C}_4\text{H}_9\text{OH}$	-0.098	+0.0040	+0.52	-21.74	-7.99	-143.6	-13.10	-2.0	-20.0
$\text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$	n.- $\text{C}_4\text{H}_9\text{OH}$	-0.106	+0.0090	+1.18	-21.16	-5.46	-65.1	-13.60	-0.65	-6.5
CH_3COOH	n.- $\text{C}_3\text{H}_7\text{OH}$	+0.245	-0.0147	-1.61	-6.56	+0.24	+1.42	-11.50	+1.05	+6.7

(-1.6 up. n 0.4)

in the case of highly associated substances (glycols), the positive sign of $\Delta\epsilon_{1,2}$, as well as the noticeably lower than expected value of $\Delta\eta_{1,2}$ (Table 5), all testify to the fact that when the discussed compounds are mixed there occurs not only a partial destruction of the complexes of the associated component (if in general it does occur), but also possible processes, causing, especially for $\rho_{1,2}$ and in certain cases also $\epsilon_{1,2}$, a complete compensation of the effect of the decomposition of the complexes into the individual molecules. It is possible for these processes to be associated not only with the formation of complexes between the molecules of the different components of the mixture, but also with a distribution of the complexes (undecomposed or newly formed) in the mixture. Because of the large size and different shapes and cohesive forces of the complexes, their presence in the mixture instead of the molecules can cause more substantial and qualitatively different changes in the function of the distribution and structure of the components in the mixture [2]. The nearly "ideal" behavior of a mixture composed of two such substances as acetic acid and n-propyl alcohol, associated in the pure liquid, is apparently also explained by a compensation of the different effects on mixing.

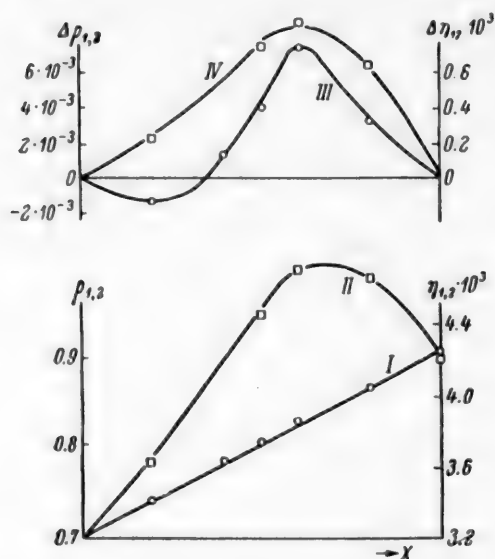


Fig. 7. $\rho_{1,2}$, $\eta_{1,2} \cdot 10^3$, $\Delta\rho_{1,2}$ and $\Delta\eta_{1,2}$ of mixture $\text{HCOOC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{NHC}_2\text{H}_5$. I) $\rho_{1,2}$; II) $\eta_{1,2} \cdot 10^3$; III) $\Delta\rho_{1,2}$; IV) $\Delta\eta_{1,2} \cdot 10^3$.

mixtures ethyl formate-diethylamine and acetic acid-n-propyl alcohol, changes in the signs of respectively $\Delta\rho_{1,2}$ and $\Delta\eta_{1,2}$ are observed with change in the concentration. In the case of the first mixture the curve $\eta_{1,2}-X_1$ passes through a maximum; a shallow minimum on the curve $\epsilon_{1,2}-X_1$ exists for the mixture n-propyl alcohol-acetone. In this connection the indicated peculiarities are observed for one of the studied properties of the mixture and are absent for the other properties of the same mixture. Apparently, also in the case of mixtures of nonassociated isoperiodic compounds it is possible to have a change in the structure of the components in the mixture, the effect of which exerts different influence on various properties of the mixtures.

SUMMARY

1. The density ($\rho_{1,2}$), viscosity ($\eta_{1,2}$) and dielectric permeability ($\epsilon_{1,2}$) values of twenty-one binary mixtures, composed of components belonging to the same series of isoperiodic compounds, were measured.
2. In the main, the $\rho_{1,2}$ and $\eta_{1,2}$ values of mixtures composed of members of the same isoperiodic series, non-associated in the pure liquid, change proportionally to the dipole moment $\mu_{1,2}$ of the mixture, while their $\epsilon_{1,2}$ changes proportionally to $\mu_{1,2}^2$.
3. For mixtures containing components, associated in the pure liquid due to hydrogen bonding, there occurs, as a rule, on mixing, a substantial change in the structure (parameters of interaction, number of neighbors, angles of orientation) of the starting pure components.

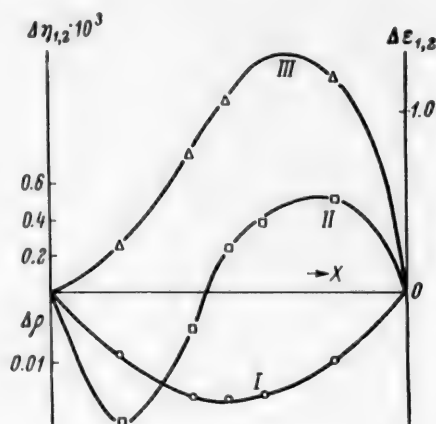


Fig. 8. $\Delta\rho_{1,2}$ (I), $\Delta\eta_{1,2}$ (II), and $\Delta\epsilon_{1,2}$ (III). Mixture $\text{CH}_3\text{COOH} + n\text{-C}_3\text{H}_7\text{OH}$.

For most of the studied mixtures (including the nonassociated substances) the curves $\Delta y_{1,2}-X_1$ are unsymmetrical (Figs. 4-6), and specifically the maximum $\Delta y_{1,2}$ does not correspond to the mixture where $X_1 = X_2 = 0.5$, while $\Delta y_{1,2}$ at $X_1 = 0.2$ is not equal to $\Delta y_{1,2}$ at $X_2 = 0.2$ [14]. For the

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ASSOCIATION AND DEPENDENCE ON CONCENTRATION OF PROPERTIES OF BINARY MIXTURES OF ORGANIC COMPOUNDS

IV. COMPOUNDS WITH CLOSE DIPOLE MOMENTS OF THE MOLECULES

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In connection with studying the character of the influence of molecular association on the concentration dependence of various properties of binary mixtures ($y_{1,2}$) it seems of interest to examine the behavior of mixtures composed of compounds, the molecules of which have close or the same dipole moments, but which differ significantly in shape, size or polarizability and mass. We measured the values of the density ($\rho_{1,2}$), viscosity coefficients ($\eta_{1,2}$) and dielectric permeability ($\epsilon_{1,2}$) of mixtures of this type composed of benzene, cyclohexane, n-hexane, phenol, and cyclohexanol with each other, of acetic and thioacetic acids with benzene and acetone, and also of ethylene, diethylene and triethylene glycols with acetone. The measurements were made over the entire concentration interval ranging from mole fraction $X_1 = 0.0$ to $X_1 = 1.0$, at a constant temperature (either 20 or 25°). The measurement procedure was described earlier [1]. The values of the mass (m), size (v_M), polarizability (α), shape and dipole moments (μ) of the molecules of the studied compounds are compared in Table 1. The results of our measurements (except for the cases of acetic acid and ethylene glycol in acetone, the data for which are given in [2]) are summarized in Table 2.

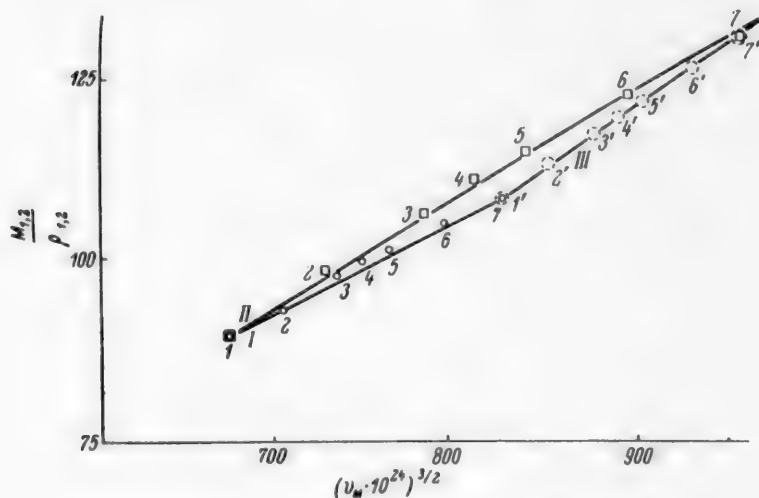
TABLE 1. Properties of Molecules of Studied Compounds

Group	Compound	$m \cdot 10^{23}$ (g)	$v_M \cdot 10^{24}$ (cm ³)	$\alpha \cdot 10^{24}$ (cm ³)	$\mu \cdot 10^{18}$	Shape
I	C ₆ H ₆	12.97	76.74	10.28	0	Lamellar
	C ₆ H ₁₂	13.97	88.02	11.02	0	The same
	n.-C ₆ H ₁₄	14.31	97.22	12.36	0	Rodlike
	C ₆ H ₅ OH	15.63	86.33	11.13	1.56, 1.45	Lamellar
	C ₆ H ₁₁ OH	16.63	93.01	11.69	1.9	The same
II	CH ₃ COOH	9.97	52.65	5.19	1.68	—
	CH ₃ COSH	12.64	64.06	8.26	—	—
III	H[OCH ₂ CH ₂]OH	10.31	57.72	5.86	2.0, 2.28	Rodlike
	H[OCH ₂ CH ₂] ₂ OH	17.62	96.65	10.26	—	The same
	H[OCH ₂ CH ₂] ₃ OH	24.94	135.58	14.62	2.3	» »

The values obtained by us for the $\rho_{1,2}$ of the mixture benzene-cyclohexane are in satisfactory agreement with the literature data [3]. Since the molecules of these components differ significantly only in size (Table 1), a regular dependence of the properties of the examined mixture on $v_{M,1,2} = X_1 v_{M,1} + (1 - X_1) v_{M,2}$ (X = mole fraction) could be expected. In accordance with the previously established total dependence of the molar volume $V = \frac{M}{\rho}$ on v_M [1], the $v_{1,2}$ value of the mixture benzene-cyclohexane increases almost linearly with $(v_{M,1,2})^{3/2}$ (Fig. 1). The magnitude and sign of the deviations from additivity of various thermodynamic properties of this mixture have repeatedly been regarded as an example of a mixture, the components of which differ only in v and interaction between whose molecules reduces only to dispersion forces [4-6]. In harmony with theory and based on our data, an expansion of the system is observed when benzene and cyclohexane are mixed (Fig. 2), in which connection the magnitude of increase in $\Delta v_{1,2}$ at $X_1 = X_2 = 0.5$ is 0.7 cm^3 (according to other data it is $+0.65 \text{ cm}^3$ [6]), which is approximately only half that calculated using the Prigogine equation [5] (under the conditions of neglecting θ^2 , $\theta\rho$ and $\theta\delta$ and equating the

TABLE 2. $\rho_{1,2}$, $\eta_{1,2} \cdot 10^3$ and $\epsilon_{1,2}$ of Binary Mixtures at 25°

Components		Property	Mole fraction of component 1						
1	2		0.0	0.2	0.4	0.5	0.6	0.8	1.0
C_6H_{12}	C_6H_6	$\rho_{1,2}$	0.8735	0.8464	0.8206	0.8137	0.8044	0.7880	0.7741
		$\eta_{1,2}$	6.01	5.81	5.88	6.06	6.29	7.02	8.41
C_6H_{12}	n.- C_6H_{14}	$\rho_{1,2}$	0.6565	0.6752	0.6963	0.7073	0.7190	0.7448	0.7741
		$\eta_{1,2}$	3.16	3.56	4.09	4.42	4.84	6.09	8.41
n.- C_6H_{14}	C_6H_6	$\rho_{1,2}$	0.8735	0.8142	0.7634	0.7389	0.7215	0.6858	0.6565
		$\eta_{1,2}$	6.01	4.69	4.00	3.77	3.59	3.34	3.16
C_6H_5OH	$C_6H_{11}OH$ (50)	$\rho_{1,2}$	0.9229	0.9453	0.9689	0.9810	0.9937	1.0210	1.0492
		$\eta_{1,2}$	80.07	64.76	52.52	49.77	46.11	40.71	33.12
		$\epsilon_{1,2}$	12.10	12.25	12.35	12.50	12.30	11.90	11.00
CH_3COOH	C_6H_6	$\rho_{1,2}$	0.8735	0.8927	0.9159	0.9305	0.9468	0.9881	1.0452
		$\eta_{1,2}$	6.02	5.98	6.17	6.36	6.72	8.02	11.33
		$\epsilon_{1,2}$	2.10	2.20	2.58	2.70	3.15	4.45	7.15
CH_3COSH	C_6H_6	$\rho_{1,2}$	0.8735	0.9017	0.9346	0.9515	0.9700	1.0100	1.0572
		$\eta_{1,2}$	6.01	5.84	5.84	5.89	5.99	6.31	6.87
		$\epsilon_{1,2}$	2.10	3.40	5.20	6.00	7.40	10.45	14.30
CH_3COSH	CH_3COCH_3	$\rho_{1,2}$	0.7854	0.8421	0.8982	0.9254	0.9526	1.0052	1.0572
		$\eta_{1,2}$	3.42	4.05	4.79	5.11	5.51	6.24	6.87
		$\epsilon_{1,2}$	20.40	20.30	19.50	18.85	18.15	16.60	14.15
$H(CH_2CH_2O)_2OH$	CH_3COCH_3	$\rho_{1,2}$	0.7854	0.8640	0.9490	0.9813	1.0125	1.0668	1.1129
		$\eta_{1,2}$	3.31 (no boile)	6.82	16.69	26.55	43.01	111.02	278.69
		$\epsilon_{1,2}$	20.3	22.7	24.5	25.7	26.3	27.7	29.5
$H(CH_2CH_2O)_3OH$	CH_3COCH_3	$\rho_{1,2}$	0.7854	0.8987	0.9782	1.0102	1.0376	1.0810	1.1177
		$\eta_{1,2}$	3.36	10.38	27.50	44.80	71.68	170.45	374.0
		$\epsilon_{1,2}$	20.30	21.50	22.00	22.35	—	22.30	22.15

Fig. 1. Dependence of the molar volume $v_{1,2}$ at 25° on $v_{M1,2}$.

I) Benzene-cyclohexane; II) benzene-n-hexane; III) cyclohexane-n-hexane. Mole fraction of component 1: 1) 1.0, 2) 0.8, 3) 0.6, 4) 0.5, 5) 0.4, 6) 0.2, 7) 0.0.

terms δ and ρ to 0.02 and -0.08 respectively):

$$\Delta v_{1,2} = 0.25 [-60\delta^2 + 790\rho^2 - 34.5\rho\delta] = +1.28 \text{ cm}^3.$$

Relating this change in the volume on mixing with the difference in the size of the molecules of the components follows from the fact that the sign of $\Delta v_{1,2}$ coincides with the sign of the difference $v_{M1,2}^{3/2} - (X_1 v_{M1})^{3/2} - (X_2 v_{M2})^{3/2}$, while the value of $\Delta v_{1,2}$ changes symbatically with change in this difference. In contrast to the ρ , cyclohexane has a higher η than does benzene, which is caused both by a larger mass and polarizability, and possibly by certain details of the shape of its molecules. The negative sign of the $\Delta \eta_{1,2}$ of this mixture (Fig. 3) testifies to the smaller energy of interaction between the molecules of different, rather than the same, components [7], which may be caused by the corresponding changes in the structure (interaction parameters ϵ^* and r^* , number of neighbors, character of orientation) of the components on mixing when compared with the structure in the pure liquid.

The $v_{1,2}$ values of the mixtures of n-hexane with benzene or with cyclohexane, the same as in the case of the mixture benzene-cyclohexane, increases linearly with $v_{M1,2}^{3/2}$ (Fig. 1). These components on mixing also exhibit, and nearly to the same degree (Table 3) as the benzene-cyclohexane mixture, an expansion of the system [4]. For the n-hexane-cyclohexane mixture the curve $\Delta \rho_{1,2} - X_1$ (Fig. 2), in contrast to the other thermodynamic properties [8], and also in contrast to the curve $\Delta \eta_{1,2} - X_1$ (Fig. 3), is almost strictly symmetrical. In contrast to the $\rho_{1,2}$ for these mixtures, a noticeable increase in the values of $\Delta \eta_{1,2}/\eta_{1,2}$ is observed.

Obviously in the case of $\rho_{1,2}$ the influence of a difference in the shape of the molecules has limited significance when compared with the influence of a difference in their size; $\eta_{1,2}$ proves to be much more sensitive to a difference in the shape of the molecules, which is manifested in a more negative deviation of their values from additivity.

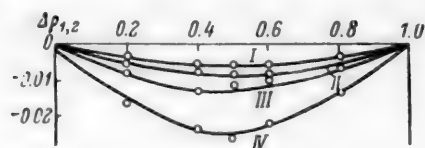


Fig. 2. Change in $\Delta \rho_{1,2}$ with the concentration. I) Phenol-cyclohexane; II) n-hexane-cyclohexane; III) benzene-cyclohexane; IV) benzene-n-hexane.

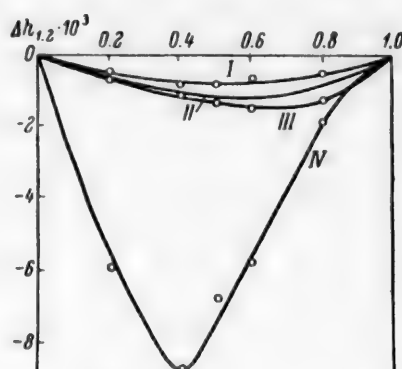


Fig. 3. Change in $\Delta \eta_{1,2} \cdot 10^3$ with the concentration. I) n-Hexane-benzene; II) benzene-cyclohexane; III) n-hexane-cyclohexane; IV) phenol-cyclohexanol.

Similar to the molecules of benzene and cyclohexane, the molecules of phenol and cyclohexanol exhibit nearly the same shape, mass, polarizability and dipole moment, differing essentially only in size (Table 1). Despite the association of the phenol and cyclohexanol molecules in the pure liquid, this mixture behaves not only qualitatively (the same signs of $\Delta \rho_{1,2}$ and $\Delta \eta_{1,2}$), but also quantitatively like the benzene-cyclohexane mixture. In addition, this mixture, in its values of $\Delta \rho_{1,2}/\rho_{1,2}$ and $\Delta \eta_{1,2}/\eta_{1,2}$, behaves even more "ideally" than the benzene-cyclohexane mixture. In this respect the phenol-cyclohexanol mixture approaches the other mixture of two compounds studied by us, showing association in the pure liquid because of hydrogen bonding between the molecules, namely, acetic acid and n-propyl alcohol [2]. Obviously, also in the case of the phenol-cyclohexanol mixture a superimposition of a number of effects takes place on mixing: a destruction of the complexes, the formation of complexes between the molecules or the complexes of the components of the mixture, a change in the structure of the components in the mixture, etc. The complexity of the mixing process in the given case also follows from the fact that the curve $\epsilon_{1,2} - X_1$ of the examined mixture is somewhat convex to the $\epsilon_{1,2}$ axis and passes through a maximum at $X_1 \sim 0.5$ (while for the acetic acid-propyl alcohol mixture the curve $\epsilon_{1,2} - X_1$ has, in contrast, a minimum).

As had been previously shown [2], in mixtures of isoperiodic compounds, with one component exhibiting association in the pure liquid, the effect of association is manifested in the presence, as a rule, of a substantial contraction of the system and a sharp decrease in the viscosity when compared with the additive value. The data for the mixtures of the diethylene and triethylene glycols with acetone (Table 2) indicate the generality of these association effects. Actually, a contraction of the system is also observed for these mixtures, in which connection the values of $\Delta \rho_{1,2}$ and $\Delta \rho_{1,2}/\rho_{1,2}$ increase with increase in the number of OCH_2CH_2 groups in the glycol molecule; also for them $\Delta \eta_{1,2}$ is negative, in which connection the absolute value of $\Delta \eta_{1,2}$ (in contrast to $\Delta \eta_{1,2}/\eta_{1,2}$) increases sharply with increase

TABLE 3. Values of $\Delta y_{1,2}/y_{1,2}$ at $X_1 = X_2 = 0.5$ and Temperature 25°

Mixture	$\Delta v_{1,2}$ (cm ³)	$\frac{\Delta \rho_{1,2}}{\rho_{1,2}} \cdot 10^3$	$\frac{\Delta \eta_{1,2}}{\eta_{1,2}} \cdot 10^3$	$\frac{\Delta \epsilon_{1,2}}{\epsilon_{1,2}} \cdot 10^3$	Maximum $\Delta y_{1,2}$ at x_1 for		
					$\rho_{1,2}$	$\eta_{1,2}$	$\epsilon_{1,2}$
$C_6H_6 + C_6H_{12}$	+0.70	-1.2	-18.9	—	0.4	0.6	—
$C_6H_6 + C_6H_{14-n}$	+0.84	-3.5	-21.4	—	0.5	0.4	—
$C_6H_{12} + C_6H_{14-n}$	+0.45	-1.1	-30.7	—	0.5	0.6	—
$C_6H_5OH + C_6H_{11}OH$ (50°)	—	-0.51	-13.7	+ 7.6	0.5	0.4	0.5
$C_6H_6 + CH_3COOH$	+0.79	-3.1	-36.3	-70.3	0.6	0.6	0.6
$C_6H_6 + CH_3COSH$	—	-1.4	-9.3	-35.8	0.5	0.6	0.5
$CH_3COCH_3 + CH_3COOH$	+0.68	-0.74	-20.0	—	0.6	0.5	—
$CH_3COCH_3 + CH_3COSH$	-0.47	+0.44	-0.40	+ 8.4	0.5	—	0.5
$CH_3COCH_3 + H[OCH_2CH_2]OH$	-0.87	+0.90	-537	- 6.0	0.4-0.5	0.6	0.6
$CH_3COCH_3 + H[OCH_2CH_2]_2OH$	-0.98	+3.28	-431	+ 3.1	0.4	0.6	0.5
$CH_3COCH_3 + H[OCH_2CH_2]_3OH$	-1.08	+5.81	-298	+ 5.0	0.4	0.6	0.5

in the number of OCH_2CH_2 groups. For the mixtures of the diethylene and triethylene glycols with acetone, in contrast to the ethylene glycol-acetone mixture and other mixtures of isoperiodic compounds, containing one component associated in the pure liquid, an increase in $\epsilon_{1,2}$ (for the mixture containing triethylene glycol this is also manifested in the presence of a maximum on the curve $\epsilon_{1,2}-X_1$) when compared with the additive value is observed, in which connection the value of $\Delta\epsilon_{1,2}/\epsilon_{1,2}$ also increases with increase in the number of OCH_2CH_2 groups in the molecule.

The asymmetry of the $\Delta y_{1,2}-X_1$ curves of all of the studied properties also shows noticeably increase for the mixtures of the diethylene and triethylene glycols with acetone (Fig. 4). The presence of contraction, and not of dilatation, the same as an increase, and not a decrease (when compared with the additive value) in the values of $\epsilon_{1,2}$, testifies to the superimposition of the effects, compensating the destruction effect in the mixture of complexes, formed by the glycols in the pure liquid, when the examined substances are mixed. These effects may be replacement of the destroyed complexes of the glycol molecules by the complexes of the latter with the acetone molecules and a change in the structure of the components in the mixture in connection with the peculiarities of the complexes of the molecules — their size, shape, cohesive forces. That the latter is present is evidenced by the dependence of $\Delta y_{1,2}/y_{1,2}$, the sign of $\Delta\epsilon_{1,2}$, the degree of asymmetry of the $\Delta y_{1,2}-X_1$ curves, etc., on the number of OCH_2CH_2 groups in the glycol molecule (and consequently, in the glycol complex).

The tendency of acetic acid, in contrast to thioacetic acid, to form dimers, manifested in the first having a higher viscosity and a lower dielectric permeability when compared to the second, also finds its reflection in the properties of the mixtures of these acids with benzene (Table 2, Fig. 5). In benzene, where the acetic acid dimers are retained, the values $\Delta\rho_{1,2}/\rho_{1,2}$, $\Delta\eta_{1,2}/\eta_{1,2}$ and $\Delta\epsilon_{1,2}/\epsilon_{1,2}$ are noticeably higher when compared with the same values for the benzene-thioacetic acid mixture. It is natural to expect this because of the considerably greater difference between the properties of the acetic acid complexes and the benzene molecules than between the molecules of the latter and the thioacetic acid molecules. The absence of destruction of the acetic acid complexes in benzene follows from the identity of the signs of the studied $\Delta y_{1,2}/y_{1,2}$, the character of the $y_{1,2}-X_1$ curves (Fig. 5), and the $\eta_{1,2}-X_1$ curve (passage through a minimum) for the mixtures of both acids. In acetone the behavior of these acids is already different. In the values of $\Delta\rho_{1,2}/\rho_{1,2}$ and $\Delta\eta_{1,2}/\eta_{1,2}$, the mixture containing thioacetic acid behaves almost like an "ideal" solution, in which connection the signs of $\Delta\rho_{1,2}$ and $\Delta\epsilon_{1,2}$ are opposite to those for its mixture with benzene. The mixture containing acetic acid exhibits noticeably higher (but having the same sign) values of $\Delta\rho_{1,2}/\rho_{1,2}$ and $\Delta\eta_{1,2}/\eta_{1,2}$ than does the acetic acid-benzene mixture. If it is assumed that a nearly complete destruction of the acetic acid dimers occurs in acetone, then the observed values of $\Delta\rho_{1,2}$ and $\Delta\eta_{1,2}$ testify to the substantial compensation of this destruction effect by the apparent replacement of the complexes composed of acid molecules by the complexes formed between the acid and acetone molecules. The positive signs of $\Delta\rho_{1,2}$ and $\Delta\epsilon_{1,2}$, as well as the sharp decrease in the absolute values of $\Delta\eta_{1,2}$ for the acetone-thioacetic acid mixture, are possibly due to the formation of weak $S-H \cdots O=C$ bonds.

The above data also clarify to some degree the problem of the reasons for the formation of minima or maxima on the $y_{1,2}-X_1$ curves in mixtures of nonassociated compounds. The arising of minima on the $\eta_{1,2}-X_1$ curves in the case of the mixtures benzene-cyclohexane and benzene-thioacetic acid (their other properties do not exhibit a minimum) is associated with the fact that the $\Delta\eta_{1,2}$ values of these mixtures are relatively greater than the difference in

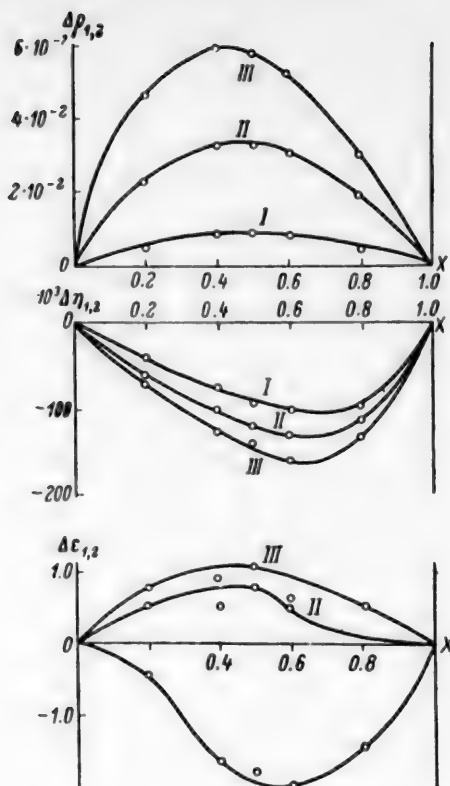


Fig. 4. $\Delta\rho_{1,2}$, $\Delta\eta_{1,2} \cdot 10^3$ and $\Delta\epsilon_{1,2}$ of mixtures of glycols with acetone. I) Ethylene glycol + acetone; II) diethylene glycol + acetone; III) triethylene glycol + acetone.

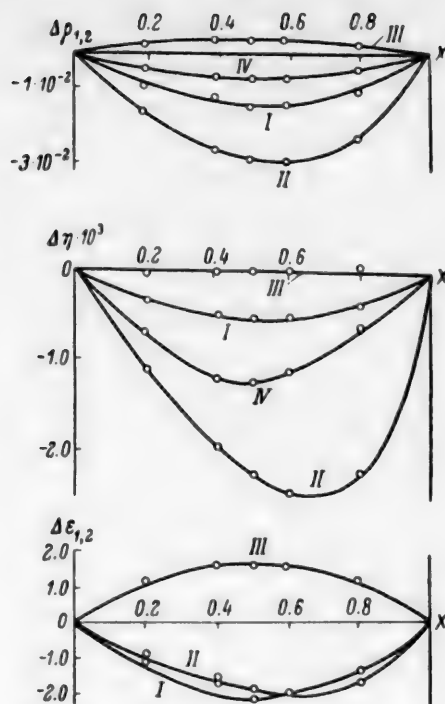


Fig. 5. $\Delta\rho_{1,2}$, $\Delta\eta_{1,2} \cdot 10^3$ and $\Delta\epsilon_{1,2}$ of mixtures containing acetic acid or thioacetic acid at 25°. I) Thioacetic acid + benzene; II) acetic acid + benzene; III) thioacetic acid + acetone; IV) acetic acid + acetone.

the η values of the pure components. Evidence of this is the absence of a minimum for the cyclohexane-hexane mixture and its substantially lower manifestation in the case of the acetic acid-benzene mixture. Obviously, the presence of extremes for the individual properties of certain mixtures is in no way related to the formation of chemical compounds between the molecules of the components, but instead is caused by a superimposition of the effect of deviations from the additive value of a given property, in turn also depending on the changes in the structure of the components of the mixture.

SUMMARY

1. The following values were measured: the density ($\rho_{1,2}$) and viscosity ($\eta_{1,2}$) of mixtures of benzene, cyclohexane and n-hexane with each other, and the $\rho_{1,2}$, $\eta_{1,2}$ and dielectric permeability ($\epsilon_{1,2}$) of the mixtures phenol-cyclohexanol, benzene-acetic acid, benzene-thioacetic acid, and also of the mixtures of acetone with thioacetic acid, diethylene glycol, and triethylene glycol.
2. The molar volume of the mixtures benzene-cyclohexane, benzene-n-hexane and cyclohexane-n-hexane increases linearly with increase in the values of $[X_1 v_{M,1} + (1 - X_1) v_{M,2}]^{2/3}$ (v_M is the size of the molecules of the components). The deviation of the molar volume from additivity ($\Delta v_{1,2}$) for these mixtures coincides in sign and changes symbatically with the difference $v_{M,1,2}^{2/3} - [(X_1 v_{M,1})^{2/3} + (X_2 v_{M,2})^{2/3}]$.
3. The contraction ($-\Delta w_{1,2}$) and positive value of $\Delta\epsilon_{1,2}$ for mixtures of acetone with glycols testify to the presence on mixing of processes causing a compensation of the effect of the possible destruction of the complexes formed between the glycol molecules.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

ISOQUINOLINE COMPOUNDS

II. DERIVATIVES OF AN ISOMER OF SALSOLINE

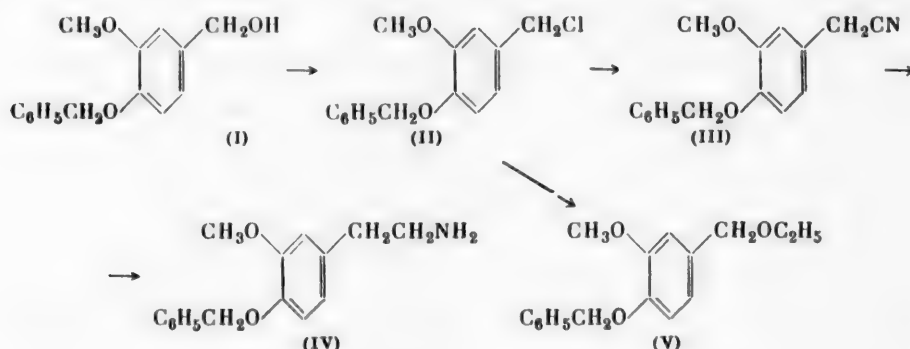
I. T. Strukov

The S. Ordzhonikidze All-Union Scientific Research Chemico-Pharmaceutical Institute

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Derivatives of 6-methoxy-7-hydroxy-3,4-dihydro- and 6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline substituted in position 1 may be successfully synthesized if a sufficiently convenient method of preparing 3-methoxy-4-benzyloxyphenylethylamine is available. Although a method for its preparation, described by L. V. Volkova [1], appeared more convenient than a synthesis from vanillin through ferulic acid [2,3], it was really not very good. We therefore introduced a series of changes into the syntheses of 3-methoxy-4-benzyloxybenzyl chloride (II) and 3-methoxy-4-benzyloxybenzyl cyanide (III), which guaranteed a good yield of 3-methoxy-4-benzyloxyphenylethylamine (IV), based on vanillin, and it became available for further use.



In contrast to the usual method [1], 3-methoxy-4-benzyloxybenzyl chloride was obtained by the interaction of benzyivanillyl alcohol and thionyl chloride in chloroform solution. After removal of the chloroform and excess thionyl chloride, the oil which remained was dissolved in chloroform and washed with a solution of sodium bicarbonate; compound (II) was thus obtained in pure form. In order to obtain 3-methoxy-4-benzyloxybenzyl cyanide we considerably decreased the excess of sodium cyanide, replaced the aqueous alcohol medium in which the reaction was previously carried out with a mixture of dioxane and water, and in this way eliminated the side reaction which forms 3-methoxy-4-benzyloxybenzyl ethyl ether (V). The sodium cyanide must be of high quality, since any sodium carbonate impurity in it facilitates the polymerization of the nitrile and the formation of benzyivanillyl alcohol.

The synthesis of 6-methoxy-7-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline was described previously [4]. A description is given in this work of more elegant procedures for the preparation of the individual partial products: 6-methoxy-7-benzyloxy-1-methyl-3,4-dihydroisoquinoline and 6-methoxy-7-benzyloxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline. The iodomethylate of 6-methoxy-7-benzyloxy-1-methyl-3,4-dihydroisoquinoline was reduced with sodium borohydride in 90% methanol [5]. The reduction process apparently goes at the expense of the interaction of the iodomethylate with hydrogen at the moment of its formation. The benzyl group was finally removed from the 6-methoxy-7-benzyloxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline by heating the latter with 20% hydrochloric acid.

EXPERIMENTAL

3-Methoxy-4-benzyloxybenzyl chloride (II). A mixture of 50 g of benzylvanillyl alcohol and 100 ml of chloroform was placed in a 500 ml, round-bottomed flask equipped with a stirrer, dropping funnel, and a distillation tube, the flask was standing in a water bath. The mixture was cooled to 10-15° and 50 ml of freshly distilled (over sulfur) thionyl chloride was gradually added through the dropping funnel; stirring was continued for 1 hr at this temperature. The chloroform and thionyl chloride were removed *in vacuo* at a bath temperature of 40-50°. The residue was dissolved in 100 ml of chloroform; a solution of sodium bicarbonate was gradually added with stirring until there was no acid reaction to Congo. The chloroform solution was washed with water, dried over magnesium sulfate, decolorized with charcoal, and filtered; the chloroform was evaporated *in vacuo*. The residue was dissolved in 20 ml of chloroform and warmed; to the warm solution was added 100 ml of benzene and the flask was placed in a refrigerator. The precipitate was filtered off on the following day, washed with benzene, and dried. The yield was 40 g.

From the mother liquor after removal of the solvent and fractionation of the residue, there was collected a fraction with a boiling point of 185-190° at 1 mm; this was crystallized from a mixture of chloroform and benzene (1:4). An additional 6 g of 6-methoxy-4-benzyloxybenzyl chloride was obtained. The total yield was 46 g (85.4%). The melting point was 72-74°.

3-Methoxy-4-benzyloxybenzyl cyanide (III). Into a 500 ml, round-bottomed flask furnished with a stirrer and thermometer was introduced 15 g of 86% sodium cyanide (approximately 40% excess), 100 ml of water, and 50 ml of dioxane. The mixture was stirred and warmed to 55-60°; 50 g of 3-methoxy-4-benzyloxybenzyl chloride was added in a 30 min period, and the mixture was stirred for 2 hrs. The reaction mixture was placed in a separatory funnel and treated with 500 ml of water and 200 ml of chloroform. The lower layer was separated, washed with water, dried over magnesium sulfate, and the chloroform was evaporated *in vacuo*. The brown oil which remained was dissolved in 80 ml of alcohol, a seed was introduced, and the flask was placed in a refrigerator overnight. The solid which separated was filtered off and washed with alcohol. The yield was 25.5 g.

The mother liquor was evaporated *in vacuo* on a water bath and the residual oil was distilled at 1 mm; a fraction was collected which boiled at 195-205°. This was dissolved in 2 volumes of alcohol and placed in the refrigerator, yielding an additional 5 g. The yield of 3-methoxy-4-benzyloxybenzyl cyanide was 30.5 g (63.3%). The melting point was 67-68° (from alcohol).

3-Methoxy-4-benzyloxyphenylethylamine (IV). A mixture of 60 g of 3-methoxy-4-benzyloxybenzyl cyanide, 5 g of nickel catalyst (washed with methanol), and 200 ml of methyl alcohol was placed in a 500 ml, stainless steel, rotating autoclave and was saturated with ammonia at 0°. Hydrogen was added to a pressure of 80 atmospheres and the autoclave was heated at 100° for 1 hr. The pressure rapidly dropped to 36 atmospheres. The hydrogen was released from the autoclave on the following day and the reaction mixture was filtered from the catalyst. The methanol and ammonia were removed and the residual oil was distilled *in vacuo*. The boiling point was 190-195° at 2 mm. The yield was 55 g (91.0%). 3-methoxy-4-benzyloxyphenylethylamine is a colorless oil which rapidly crystallizes.

6-Methoxy-7-benzyloxy-1-methyl-3,4-dihydroisoquinoline. A mixture of 50 g of N-(3-methoxy-4-benzyloxyphenylethyl)-acetamide, 500 ml of dry chloroform and 70 g of finely divided phosphorus pentachloride was placed in a 1 liter, round-bottomed flask furnished with a reflux condenser. The reaction began immediately and a yellow crystalline precipitate gradually formed. The reaction mixture was heated at 50-60° for 1 hr and was then placed in the refrigerator; the precipitate was filtered off, washed several times with chloroform, and was then recrystallized from 100 ml of alcohol. The yield of the hydrochloride of 6-methoxy-7-benzyloxy-1-methyl-3,4-dihydroisoquinoline was 40.5 g.

A considerable quantity of the isoquinoline compound remained in the chloroform solution. In order to isolate this material, the chloroform solution was gradually poured into 500 ml of a 25% aqueous solution of ammonia with cooling and shaking. The chloroform layer was separated, washed with water, and with 250 ml of 2% hydrochloric acid; it was dried over magnesium sulfate and the chloroform was distilled away. The residue was dissolved in 20 ml of alcohol and the solution was let stand to crystallize. An additional 7.5 g of the hydrochloride was obtained. The melting point was 190-191°. The total yield was 48 g (90.0%).

An aqueous ammonia solution was gradually added with cooling to a solution of 8.1 g of the hydrochloride dissolved in 100 ml of warm water. The base immediately separated in a crystalline condition. The yield was 7 g (97%). The melting point was 87-88°.

6-Methoxy-7-benzyloxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline. In a 2 liter, 3-necked, round-bottomed flask equipped with a stirrer and thermometer were placed 50 g of the iodomethylate of 6-methoxy-7-benzyloxy-1-methyl-3,4-dihydroisoquinoline, 1 liter of methanol, and 100 ml of water; at 20-25° during 1 hr there was gradually added 12 g of sodium borohydride. The mixture was stirred for 1 hr. The methanol was distilled away. The residue was treated with 200 ml of water and 25 ml of 25% ammonia solution; the base which separated was extracted 3 times with chloroform. The solution was dried over magnesium sulfate and the chloroform was removed. To the residual oil dissolved in 60 ml of alcohol was added an alcohol solution of hydrogen chloride until a weakly acid reaction was obtained with Congo. The flask was then placed in a refrigerator. The solid which separated was filtered off and dried in a vacuum desiccator. The yield was 32.5 g (82.3%). The melting point was 191-193° (from alcohol). The base itself was obtained by treatment of a solution of the hydrochloride in water with ammonia; it was extracted with ether and twice recrystallized from a small quantity of ether. The melting point was 78-79°.

Found %: C 76.81, 77.00; H 7.89, 7.53; N 4.5. $C_{19}H_{23}O_2N$. Calculated %: C 76.73; H 7.79; N 4.71.

Hydrochloride of 6-methoxy-7-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline. Fifty g of 6-methoxy-7-benzyloxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline was heated with 500 ml of 20% sulfuric acid at 80-90° for 2 hours. The hydrochloride residue was gradually dissolved and precipitated as a layer of benzyl chloride. The reaction mass was evaporated in an aqueous bath in a vacuum drier whereupon the benzyl chloride was distilled together with the water. The residue, in the form of a very thick, uncrystallizable mass, was treated with 100 ml of isopropyl alcohol and again distilled in vacuum. The residue was recrystallized with 250 ml of dry isopropyl alcohol and the hydrochloride of 6-methoxy-7-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline was obtained. M.p. 190-192°. Yield 30.8 g (75.5%). The base separated from the hydrochloride with the use of ammonia had m.p. 148-150°.

SUMMARY

The methods for obtaining 3-methoxy-4-benzyloxybenzyl chloride and 3-methoxy-4-benzyloxybenzyl cyanide were improved. We obtained from these above-mentioned methods the following isoquinoline compounds: 6-methoxy-7-benzyloxy-1-methyl-3,4-dihydroisoquinoline and 6-methoxy-7-benzyloxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline.

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THE CHEMISTRY OF POLYMYXIN M

III. A PARTIAL HYDROLYSIS OF POLYMYXIN M

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As was shown in the preceeding communications of this series [1,2], the native antibiotic polymyxin M [3] is a peptide which is apparently composed of 6 α , γ -diaminobutyric acid residues, 3 threonine residues, 1 leucine residue, and a fatty acid which is possibly 6-methyloctanoic acid. The molecule of polymyxin M contains 5 free amino groups which appeared to be the γ -amino groups of the α , γ -diaminobutyric acid.

After establishing the qualitative and quantitative amino acid composition of the molecule, the next problem is to elucidate the sequential order of the amino acids. Since polymyxin M does not have α -amino or carboxyl end-groups, it is impossible to use methods which sequentially split off amino acids from the amino or the carboxyl end of the molecule such as are ordinarily used for the establishment of the structure of peptides. To study the structure of polymyxin M it is necessary, therefore, to first cleave the antibiotic into individual peptides, separate these, and determine their structure; one may then reconstruct the molecule of polymyxin M.

The communication is devoted to the first stage of the study of the structure of polymyxin M—to a partial hydrolysis of the antibiotic and a fractionation of the hydrolyzate. In addition, the results of the investigation of one of the hydrolyzate fractions are examined and the character of the fatty acid bond in the molecule is discussed.

The hydrolysis of polymyxin M with 6 N hydrochloric acid at 100° occurs very rapidly according to our observations, and after several hours the antibiotic is almost completely separated into the component amino acids. It is highly probable that the instability of the molecule is associated with the presence of the considerable quantity of threonine in it. In order to slow down the hydrolysis we carried it out at 40°. Chromatographic and electrophoretic analyses of the hydrolyzate showed that the action of 6 N hydrochloric acid for 3.5 days was most favorable for the hydrolysis.

A paper chromatographic analysis of the partial hydrolyzate of polymyxin M in the mixture butanol-water-acetic acid (4:5:1) separated three principal polypeptide zones: 1) polypeptides which moved together with leucine or somewhat faster (designated subsequently by the letter L); 2) polypeptides which are situated close to threonine (zone T); and 3) polypeptides which appear on the chromatogram close to α , γ -diaminobutyric acid (zone D).

Chromatography on powdered cellulose was used for the preparative separation of the mixture of peptides and amino acids. Preparative chromatography on cellulose columns is often used at the present time. However, the experimenter is deprived in this case of the possibility of observing the progress of the separation of the mixture. In our laboratory we have for many years successfully used preparative horizontal chromatography on cellulose powder. The separation of the mixture is easily controlled by the use of this method. The behavior during horizontal preparative chromatography is very close to that observed with analytical chromatography. May we suggest that this convenient method will find use in laboratory practice.

We thus separated the fractions L, T, and D from the partial hydrolyzate of polymyxin M by preparative chromatography.

A further investigation of fraction L showed that it consisted of at least three components; these were separated chromatographically by the system butanol-water-acetic acid (144:43:13). Those fractions designated as L₁, L₂, and L₃ were separated by preparative chromatography on paper sheets. Fraction L₃ appeared to be free leucine. Fraction

L₁, which moved noticeably more rapidly on the chromatogram than leucine, is apparently a comparatively complex peptide. This fraction was not studied in greater detail. The chromatographic behavior of fraction L₂, which occupied a middle position on the chromatogram between L₁ and L₃, indicated that it possessed hydrophobic properties since it is known that amino acids and peptides with non-polar side chains move rapidly during chromatography. After complete hydrolysis of the fraction L₂ only α , γ -diaminobutyric acid was observed chromatographically. One may conclude from this that the fraction L₂ contains some derivative of diaminobutyric acid which has hydrophobic properties. During electrophoresis L₂ behaves like a neutral amino acid; therefore one of the amino groups of the diaminobutyric acid of the derivative under examination is blocked by an acyl residue. From a consideration of these facts one may propose that the fraction L₂ is composed of α , γ -diaminobutyric acid which is acylated at one of the amino groups by a fatty acid residue.

In order to confirm this proposal and simultaneously to establish which amino group of the diaminobutyric acid is acylated, we carried out a chromatographic and electrophoretic comparison of the fraction L₂ with the compounds α -caprylyl- α , γ -diaminobutyric acid and γ -caprylyl- α , γ -diaminobutyric acid [4] which we synthesized in our laboratory. The replacement of the 6-methyloctanoic acid of polymyxin M by caprylic acid was made because the former is difficultly accessible. Fraction L₂ behaved exactly like α , γ -diaminobutyric acid and not like the γ -isomer. A dinitrophenylation of fraction L₂ was carried out. The dinitrophenyl derivative was then hydrolyzed. An electrophoretic investigation of the hydrolyzate showed that it contained γ -dinitrophenyl- α , γ -diaminobutyric acid. Consequently, in the original compound the γ -amino group of the diaminobutyric acid was free and the α -amino group was acylated.

It was thus established that in polymyxin M the fatty acid is joined by an amide linkage to the α -amino group of the one of the α , γ -diaminobutyric acid residues. It should be remarked that in polymyxin C the α , γ -diaminobutyric acid is similarly acylated at the α -amino group by 6-methyloctanoic acid [5].

EXPERIMENTAL

1. The partial hydrolysis of polymyxin M. The sulfate of polymyxin M, 900 mg. was dissolved in 50 ml of 6 N hydrochloric acid. The solution was kept in a thermostat at 40° for 3.5 days. The hydrolyzate was twice extracted with ether, the aqueous layer was evaporated in vacuo to dryness, an excess of hydrochloric acid was added and removed many times by distillation with water in vacuo at 25°. The fractionation was carried out with the dry residue.

2. Preparative horizontal chromatography on powdered cellulose. The chromatographic separation of the mixture was carried out in a vinyl plastic vessel of 30 cm length, 6.5 cm. width, and 2.5 cm height. The vessel was placed on two crystallizing dishes of 500 ml volume. Over each end of the vessel were hung 20 slips of chromatographic paper measuring 6.5 x 10 cm. One end of each of these slips touched the bottom of the vessel and the other end hung into a crystallizing dish. A well-mixed slurry of 40-60 g of powdered cellulose in 100-150 ml of a butanol-water-acetic acid (4:1:1 by volume) mixture was poured into the vessel. The solvents immediately began to flow from the vessel into the crystallizing dishes by way of the paper chromatographic slips. There remained in the vessel after several hours an evenly moist layer of powdered cellulose. At one end of the vessel a channel 0.4-0.7 cm in width was dug with a spatula; it was separated by 0.5 cm from the side walls of the vessel. The groove was filled with a thick paste obtained by the addition of dry powdered paper to a solution of the mixture to be fractionated. The crystallizing dish closest to the zone of the mixture was filled with the solvent butanol-water-acetic acid 4:1:1. A 1-2 cm layer of the solvent was left in the other crystallizing dish. Because of the difference in the levels there occurred a transfer of solvent from one crystallizing dish to the other, and this led to the chromatographic separation of the components of the mixture. The solvent level in the crystallizing dish was maintained constant. To check the course of the separation a piece of chromatographic paper was carefully laid on the moist, powdered cellulose layer. It was removed after 1 min, dried, and tested with ninhydrin. After a separation of the zones had been attained, the corresponding portions of the moist layer were removed from the vessel and the cellulose powder was carefully washed with water on a filter. The filtrate was evaporated in vacuo at 30°.

The chromatographic separation of the partial hydrolyzate of polymyxin M was carried out in two batches of 400 mg each. The experiments required 4 days. Three peptide fractions were isolated. These were the rapidly moving fraction L-160 mg and the middle fraction T-150 mg. The third fraction D was hardly displaced. It weighed 420 mg. The total weight of the peptides was 730 mg, a yield of 91%. The fractions were cleanly separated; there were no intermediate, mixed zones.

The Length of Path of the Spot (in cm) During Electrophoresis on Paper (displacement toward the cathode)

Compound	The number of the experiment				
	1	2	3	4	5
Fraction L ₂	6.5	4	1.5	0	0
α -Caprylyl- α, γ -diaminobutyric acid	—	4	1.5	—	—
γ -Caprylyl- α, γ -diaminobutyric acid	—	3	0	—	—
α, γ -Diaminobutyric acid	11	—	—	7.5	6
Threonine	5.8	—	—	0	0

Note: The conditions of the experiment: 1) potential gradient 20 (V/cm), 2 hrs, 30% acetic acid; 2) 20 (V/cm), 5.5 hrs, buffered at pH 3.7 (2.4 ml of pyridine, 8 ml of acetic acid, 2 liters of water); 3) 23 (V/cm), 4 hrs (the same buffer as used in experiment 3 with the addition of 2 grams of copper acetate); 4) 20 (V/cm), 2 hrs, pyridine-acetate buffer at pH 5.9; 5) 20 (V/cm), 2 hrs, buffered at pH 7.0.

3. The chromatographic separation of fraction L. Fraction L gave three spots with R_f values 0.69, 0.83, and 0.93 when chromatographed on paper using the system butanol-water-acetic acid (144:43:13). In this system leucine has $R' = 0.69$. For preparative separation the fraction was spotted in the form of a long stripe on a whole sheet of chromatographic paper and chromatographed by the ascending method. At the end of the experiment a thin strip was cut from the edge of the sheet and was tested with ninhydrin. The corresponding separated zones on the remainder of the paper were cut out and eluted with water. By evaporation of the eluates *in vacuo* there were obtained 5.6 mg of fraction L₁ (R_f 0.93), 7.2 mg of fraction L₂ (R_f 0.83), and 7.7 mg of fraction L₃ (R_f 0.69). The behavior of the fraction L₃ and of leucine were identical when these substances were compared by chromatography and by electrophoresis on paper. The chromatographic behavior of this fraction was unchanged by a test hydrolysis with 6 N hydrochloric acid at 105° for 24 hrs.

4. The investigation of Fraction L₂. Only α, γ -diaminobutyric acid was observed by chromatography of the acid hydrolyzate fraction L₂. The fraction L₂ behaved exactly like α -caprylyl-L- α, γ -diaminobutyric acid when chromatographed on paper with the system butanol-water-acetic acid (144:43:13). Electrophoresis of the fraction L₂ was carried out under various conditions. The results of these experiments are presented in the table.

5. The dinitrophenylation of fraction L₂. The portion of the preparative chromatogram containing fraction L₂ was cut out and treated with a solution of fluorodinitrobenzene in alcohol (30 mg/ml). The paper strip was dried in a stream of warm air and was placed for 1 hr in a desiccator on the bottom of which was a layer of an alcoholic solution of trimethylamine. In order to remove by-products of the reaction, the strip was washed with benzene saturated with 1% acetic acid. The dinitrophenyl-peptide was eluted with 85% formic acid, the solution was evaporated to a small volume, and was spotted as a narrow stripe across a sheet of chromatographic paper (10 x 34 cm), after which electrophoresis was carried out for the removal of the unreacted peptide; the conditions were (800 V, 30% acetic acid, 75 min). The yellow stripe containing the dinitrophenyl-peptide was cut out, eluted with 6 N hydrochloric acid and the eluate was heated in a sealed ampoule for 18 hrs at 105°. The hydrochloric acid was removed *in vacuo*, the residue was dissolved in 0.1 N hydrochloric acid, and the solution was extracted with ether and butanol. The combined extracts were evaporated, the residue was dissolved in formic acid and subjected to electrophoresis on paper at 1000 V for 2.5 hrs in pyridine-acetate buffer at pH 3.7 with the addition of 0.1% copper acetate. The yellow spot of the dinitrophenyl derivative was displaced toward the cathode by 2.2 cm. Under the very same condition α -dinitrophenyl- α, γ -diaminobutyric acid moved 0.4 cm, γ -dinitrophenyl- α, γ -diaminobutyric acid moved 2.2 cm.

SUMMARY

1. Methods are described for the partial hydrolytic cleavage of polymyxin M and the fractionation of the hydrolyzate.
2. The method of horizontal preparative chromatography on powdered cellulose is described.

3. It is shown that in the polymyxin M molecule the fatty acid acylates the γ -amino group of α, γ -diaminobutyric acid.

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THE CHEMISTRY OF POLYMYXIN M

IV. THE SYNTHESIS AND PROPERTIES OF SOME POTENTIAL FRAGMENTS OF POLYMYXIN M

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The investigation of the structure of polymyxin M [1] has included: partial hydrolysis, the separation of the mixture of peptides so formed, and the identification of the fragments of the antibiotic molecule thus obtained. In order to reliably establish the structure of the peptides of the series, a synthetic approach is necessary. The molecule of polymyxin M consists of 6 α , γ -diaminobutyric acid residues, 3 threonine residues, 1 leucine residue and a fatty acid similar in properties to 6-methyloctanoic acid [2]. The task of this investigation was to synthesize some dipeptides from these amino acids. The behavior of the compounds which were obtained was investigated by chromatography and electrophoresis for the purpose of selecting the optimum conditions for their separation.

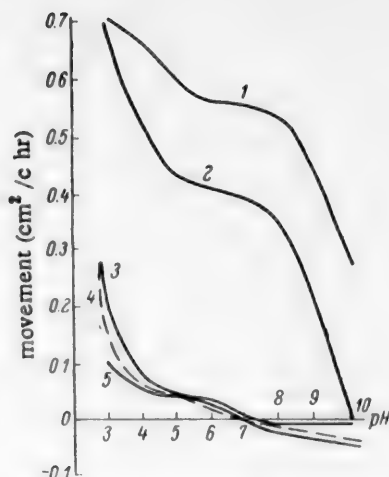
It was shown in our laboratory [3] that the partial hydrolyzate of polymyxin M contained a derivative of diaminobutyric acid which possessed hydrophobic properties. It was suggested that this derivative was the product of the acylation of α , γ -diaminobutyric acid at the α - or the γ -amino group. For proof of this proposal we synthesized some close analogues of the proposed compounds - α -n-caprylyl-L- α , γ -diaminobutyric acid and the corresponding γ -isomer, and studied their chromatographic and electrophoretic behavior. We obtained γ -n-caprylyl-L- α , γ -diaminobutyric acid by the action of the chloroanhydride of caprylic acid on the copper salt of L- α , γ -diaminobutyric acid. The α -amino group of the diaminobutyric acid was tied up in a complex with the copper and therefore could not be acylated. In order to obtain α -caprylyl-L- α , γ -diaminobutyric acid, the γ -amino group was protected by the introduction of a carbobenzoxy residue; the γ -carbobenzoxy-L- α , γ -diaminobutyric acid was then acylated with the chloroanhydride of caprylic acid, after which the carbobenzoxy group was removed by catalytic hydrogenation.

The amino acid composition of polymyxin M is dominated by diaminobutyric acid and threonine; it can be considered very probable that the diaminobutyric acid and the threonine enter sequentially into the molecule in the structure of the antibiotic. To obtain L- α , γ -diaminobutyric-D, L-threonine, we selected the azide method since it does not require the protection of the hydroxyl group of threonine. The hydrazide of α , γ -dicarbobenzoxy-L- α , γ -diaminobutyric acid was obtained by the method of Zaoral, Rudinger, and Sorm [4]. The hydrazide was converted into the corresponding azide, and this was brought into reaction with the methyl ester of D, L-threonine. The α , γ -dicarbobenzoxy-L- α , γ -diaminobutyryl-D, L-threonine so obtained was hydrolyzed with base, and the carbobenzoxy groups were then removed by catalytic hydrogenation. The free peptide was isolated in the form of the picric acid salt.

Neutral peptides as well as basic peptides are produced during the partial hydrolysis of polymyxin M. For the study of these peptides we synthesized leucylthreonine by the carbodiimide method. From carbobenzoxy-D, L-leucine and the methyl ester of D, L-threonine we obtained in high yield the methyl ester of carbobenzoxy-D, L-leucyl-D, L-threonine, which was subjected to basic hydrolysis and then to catalytic hydrogenation to convert it to the free peptide-D, L-leucyl-D, L-threonine.

All of the substances obtained were chromatographed in four solvent systems. The R_f values found can be used for the identification of the peptides of the partial hydrolyzate of polymyxin M. We also studied the electrophoretic behavior of the compounds in the pH interval 2.8 to 9.9. As is apparent from the figure, two types of curves were obtained, reflecting the dependence of the electrophoretic movement on the pH of the electrolyte: the first of these was related to substances containing two free amino groups and one carboxyl group - (α , γ -diaminobutyric acid, L-diaminobutyryl-D, L-threonine); the second, peculiar to substances containing one amino and one carboxyl group - (α - and γ -n caprylyl-L- α , γ -diaminobutyric acid, D, L-leucyl-D, L-threonine). This experiment shows that the study of the dependence of the electrophoretic movement on the pH of the electrolyte gives very valuable information for judging the acid-base properties of the compound under investigation.

EXPERIMENTAL



The dependence of the electrophoretic movement on the pH. 1) α, γ -diaminobutyric acid, 2) α, γ -diaminobutyrylthreonine, 3) α, n -caprylyl- α, γ -diaminobutyric acid, 4) leucylthreonine, 5) γ -n-caprylyl- α, γ -diaminobutyric acid.

m.p. 203–204° (with decomposition), $[\alpha]_D^{18} + 14.60$ (c 3.67 in water). The L- α, γ -diaminobutyric acid was electrophoretically and chromatographically homogeneous.

γ -n-Caprylyl-L- α, γ -diaminobutyric acid. To a solution of 1 g of the dihydrochloride of L- α, γ -diaminobutyric acid in 8 ml of water was added 2 g of copper carbonate. The intensely blue solution which was obtained after boiling under reflux for 1 hr was cooled and filtered from the excess carbonate. To the filtrate with stirring was added 2 ml of dioxane and 2 ml of n-caprylyl chloride (obtained by heating caprylic acid with thionyl chloride, b.p. 80° (10 mm)). The pH of the mixture was maintained at about 8–9 by the addition of 2 N sodium hydroxide. After 30 min the precipitate was separated by centrifugation, washed with water and with alcohol. The copper salt of γ -n-caprylyl-L- α, γ -diaminobutyric acid thus obtained was suspended in 50 ml of 0.5 N hydrochloric acid, and a stream of hydrogen sulfide was bubbled into the suspension for 2 hrs. After removal of the copper sulfide, the filtrate was evaporated to dryness *in vacuo*. A white crystalline substance was obtained, 0.61 g. The yield was 47.7%, m.p. 221° (with decomposition). The substance was recrystallized from water for analysis.

Found %: C 58.58, 58.63; H 9.79, 9.98; N 11.19, 11.31. $C_{12}H_{24}O_3N_2$. Calculated %: C 58.99; H 9.90; N 11.48.

α -n-Caprylyl-L- α, γ -diaminobutyric acid. To a solution of 1 g of γ -carbobenzoxy-L- α, γ -diaminobutyric acid in 4 ml of 1 N sodium hydroxide at 0° were added drop-wise and simultaneously a solution of 1 ml of n-caprolyl chloride in 5 ml of acetone and 9 ml of 1 N sodium hydroxide so as to maintain a pH of 9 according to a universal indicator. The mixture was stirred for 30 min at 20° and then concentrated hydrochloric acid was added with cooling until a pH of 1 was obtained. The thick yellow oil which precipitated was extracted with chloroform; the extract was dried over sodium sulfate and was evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml of methanol and was hydrogenated in the presence of palladium-black for 8 hrs; the carbon dioxide which was evolved was absorbed on solid alkali. The completeness of the cleavage of the carbobenzoxy group was tested by electrophoresis on paper. The filtrate after removal of the catalyst was evaporated *in vacuo*. The residue was washed with absolute ether. A crystalline substance weighing 0.73 g was obtained. The yield was 75%, m.p. 185.5° (with decomposition).

Found %: C 58.78, 58.67; H 10.03, 9.97; N 11.11, 11.14. $C_{12}H_{24}O_3N_2$. Calculated %: C 58.99; H 9.90; N 11.48.

The methyl ester of α, γ -dicarbobenzoxy-L- α, γ -diaminobutyryl-D, L-threonine.

To a solution of 3.2 g of the hydrazide of α, γ -dicarbobenzoxy-L- α, γ -diaminobutyric acid in a mixture of 35 ml of acetic acid and 18 ml of dilute (1:10) hydrochloric acid was added with cooling and vigorous stirring a solution of 0.67 g of sodium nitrite in 5 ml of water. The mixture was poured into 90 ml of ice water and 60 ml of ether was added. The ether layer was separated and carefully washed with ice water until a neutral reaction was obtained with Congo. The ether solution of the azide of α, γ -dicarbobenzoxy-L- α, γ -diaminobutyric acid was dried over sodium sulfate, filtered, and added to a chloroform solution of the methyl ester of D,L-threonine, which was prepared from 2 g of the hydrochloride of the methyl ester of D,L-threonine [6]. After 12 hrs the mixture was evaporated *in vacuo*; the residue was dissolved in ethyl acetate and was washed three times with 2 N hydrochloric acid, with 1 N sodium bicarbonate, and twice with a 10% solution of soda. The solution was then dried over sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from a mixture of ethyl acetate and petroleum ether. A white crystalline substance was obtained weighing 1.7 g. The yield was 36%, m.p. 134°.

Found %: C 60.11, 59.94; H 6.29, 6.23; N 8.72, 8.42. $C_{25}H_{31}O_8N_3$. Calculated %: C 59.88, H 6.23, N 8.38.

α, γ -Dicarbobenzoxy-L- α, γ -diaminobutyl-D,L-threonine. A mixture of 9.5 ml of acetone and 3.5 ml of 1 N sodium hydroxide was added to 1.5 g of the methyl ester of α, γ -dicarbobenzoxy-L- α, γ -diaminobutyl-D,L-threonine. After being shaken for 1 hr the solution was filtered and acidified to a pH of 1 with 2 N hydrochloric acid. The precipitated oil was extracted with chloroform; the extract was dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was dissolved in alcohol and water was added. The precipitated oil gradually crystallized on cooling and rubbing under a layer of the mother liquor. The crystalline material obtained weighed 1 g. The yield was 70%, m. p. 118°.

Found %: C 59.47, 59.72; H 6.19, 6.28; N 8.76, 8.76. $C_{24}H_{29}O_8N_3$. Calculated %: C 59.10; H 6.00; N 8.62.

L- α, γ -Diaminobutyl-D,L-threonine. To a solution of 0.93 mg of α, γ -dicarbobenzoxy-L- α, γ -diaminobutyl-D,L-threonine in 25 ml of methanol were added 0.4 ml of acetic acid and 100 mg of palladium-black. The mixture was shaken and hydrogenated at 20° for 14 hrs. The completeness of removal of the carbobenzoxy groups was checked by electrophoresis on paper. When the hydrogenation was completed the solution was filtered and evaporated *in vacuo*. The precipitated oil was dissolved in water and 40 ml of a 0.1 N alcoholic solution of picrolonic acid was added. Yellow crystals of the dipicrolonate precipitated. The yield was 0.98 g (67.5%), m. p. 205° (with decomposition). The substance was electrophoretically homogeneous.

Found %: C 43.44, 43.57; H 4.70, 4.80. $C_8H_{17}O_4N_3 \cdot 2C_{10}H_8O_5N_4 \cdot H_2O$. Calculated %: C 43.91; H 4.61.

The methyl ester of carbobenzoxy-D, L-leucyl-D,L-threonine. To 10 ml of an acetonitrile solution of 1.76 g of the methyl ester of D,L-threonine were added 5.2 g of dicyclohexylcarbodiimide and 4.5 g of carbobenzoxy-D,L-leucine dissolved in a mixture of anhydrous acetonitrile and dioxane. There was an immediate precipitation of dicyclohexylurea. The mixture was shaken for 5 hrs at 20° and then allowed to stand for 24 hrs. The precipitated dicyclohexylurea was filtered off and the filtrate was evaporated *in vacuo*; the residual oil was dissolved in ethyl acetate and was washed with 1 N hydrochloric acid. More dicyclohexylurea precipitated and was filtered off; the solution was then washed with a saturated solution of sodium bicarbonate and with water; it was dried over sodium sulfate and evaporated *in vacuo*. The oily residue was dissolved in absolute ether and precipitated with absolute petroleum ether. An electrophoretically homogeneous white crystalline substance weighing 6.0 g was obtained. The yield was 99%, m. p. 89-90°.

Found %: C 60.62, 60.47; H 7.73, 7.61; N 7.30, 7.44. $C_{19}H_{28}O_6N_2$. Calculated %: C 59.98; H 7.42; N 7.36.

Carbobenzoxy-D, L-leucyl-D, L-threonine. To 5.0 g of the methyl ester of carbobenzoxy-D, L-leucyl-D, L-threonine were added 15 ml of acetone and 15 ml of 1 N sodium hydroxide. After being shaken for 1 hr at 20°, the mixture was filtered and acidified to a pH of 1 with dilute hydrochloric acid. The precipitated oil was extracted with chloroform; the extract was dried over sodium sulfate and was evaporated *in vacuo*. The residual oil was crystallized by reprecipitation with water from an alcohol solution. A white crystalline substance weighing 4.4 g was obtained. The yield was 90.5%, m. p. 102-104°.

Found %: C 59.36, 59.17; H 7.31, 7.15; N 7.53, 7.65. $C_{18}H_{26}O_6N_2$. Calculated %: C 59.00; H 7.15; N 7.65.

D, L-Leucyl-D, L-threonine. To a solution of 3.3 g of carbobenzoxy-D, L-leucyl-D, L-threonine in 50 ml of methanol was added 100 mg of palladium-black, and the mixture was hydrogenated with shaking for 16 hrs at 20°; the evolved carbon dioxide was absorbed on solid alkali. The product of the reaction, which precipitated from the methanol solution, was redissolved by the addition of water. After removal of the catalyst the solution was evaporated

in vacuo; the residue was dissolved in a large quantity of water and alcohol, and was filtered and evaporated to dryness. A white crystalline substance weighing 2.1 g was obtained. The yield was 90%, m. p. 220° (with decomposition).

Found %: C 49.22, 49.04; H 8.82, 8.61; N 11.48, 11.36. $C_{10}H_{20}O_4N_2 \cdot \frac{1}{2}H_2O$. Calculated %: C 49.77; H 8.77; N 11.61.

Electrophoresis on paper. The paper electrophoreses were carried out in an apparatus described by Durrum [7]. The correction for electroendosmosis and for electrolyte intake from the electrode vessels toward the center of the paper strip, which was caused by evaporation, were determined from the movement of glucose, which was spotted in several places on the paper strip between the cathode and the starting line. A potential of 220 volts was used for the working part of the paper strip, 30.5 cm. The electrolytes used were buffered mixtures with pH of 2.8 (HCOOH-

R_f Values of the Synthetic Peptides and of the Derivatives of Diaminobutyric Acid

Substance	The solvent system			
	№ 1	№ 2	№ 3	№ 4
α -n-Caprylyl-L- α, γ -diaminobutyric acid.	0.74	0.86	0.71	0.72
γ -n-Caprylyl-L- α, γ -diaminobutyric acid	0.76	0.87	0.77	0.64
L-Diaminobutyryl-D,L-threonine	0.14	0.32	0.06	0.09
D,L-Leucyl-D,L-threonine	0.52	0.79	0.36	0.45
L- α, γ -Diaminobutyric acid	0.05	0.23	0.04	0.11
D,L-Threonine	0.20	0.52	0.12	0.19
D,L-Leucine	0.60	0.84	0.49	0.58

Note: 1) butanol-water-acetic acid (4:1:1 by volume); 2) tertiary butyl alcohol-water-formic acid (75:14:16); 3) butanol-water-acetic acid (144:43:13); 4) butanol-buffer mixture (formic acid-acetic acid-water, 15:10:2975)-water (5:2:1).

CH₃COOH-water), 4.0, 5.0, 5.8 (pyridine-acetic acid-water), 7.0 (ammonia-acetic acid-water), and 9.9 (sodium bicarbonate-sodium hydroxide-water). The current strength in all cases was 0.1-0.2 mA per cm width of the paper.

SUMMARY

Syntheses of α - and γ -n-caprylyl-L- α, γ -diaminobutyric acid, L- α, γ -diaminobutyryl-D,L-threonine, and D,L-leucyl-D,L-threonine are described. The electrophoretic and chromatographic behavior of these compounds is investigated.

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QUINONE OXIME - ARENESULFENATES

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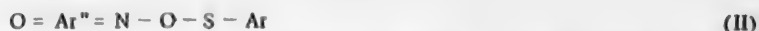
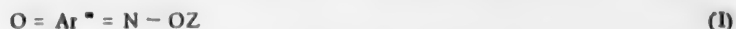
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In the preceding investigations of this series it has been shown that various esters of quinone oxime (formula I; Z is an acyl radical, Ar[•] is the corresponding quinone radical) show the so-called indophenol reaction, i.e., a blue color with phenols in an alkaline medium.



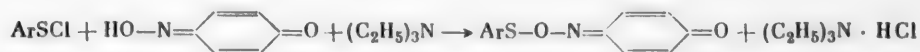
Thus the indophenol reaction is shown by quinone oxime-arenesulfonates (esters of quinone oximes and aromatic sulfonic acids) [1], esters of quinone oxime with carboxylic acids (quinone oxime-carboxylates, Z-RCO [4], dinitro-phenyl esters of quinone oximes [2], and bisulfate esters of quinone oximes [3].

Chromatographic separation of the products of the indophenol reaction has shown that the blue color is actually dependent on the formation of indophenols; basic hydrolysis occurs simultaneously to a greater or smaller degree, and quinone oximes are also formed as salts.

From observations of the indophenol reaction it was concluded that the course of the reaction was dependent on the dissociation constant of the acid ZO₂H, i.e., - the greater the dissociation constant of the acid ZO₂H, the more clearly the indophenol reaction is observed. The N-arenesulfinyl-quinoneimines conform also to this rule, although they only show the blue coloration with phenols in basic media on heating [5].

In order to study the indophenol reaction further, the present work describes the synthesis of quinone oxime-arenesulfenates (esters of arenesulfenic acids ArSOH) of general formula (II) which have not been described in the literature. Because of the instability of the arenesulfenic acids both in the free state and as salts there is no data on their dissociation constants. One can only assume that the arenesulfenic acids have dissociation constants which are higher than those of the corresponding thiophenols (ArSH). It appeared interesting to establish to what degree there occurred the concurrent heterolytic break-down of these esters at the C-O bond with the formation of the quinone oximes instead of the indophenols. The stating of this problem was conditioned by the observation that some esters of quinone oxime are quite subject to hydrolytic cleavage to the original quinone oxime and the anion of the acid (heterolytic cleavage at the C-O bond); in particular, esters of quinone oxime with some carboxylic acids show almost no indophenol reaction because of the rapid hydrolysis at the C-O bond in the basic medium.

The synthesis of the quinone oxime-arenesulfenates was accomplished by acylation of the quinone oximes with arenesulfonyl chlorides. The reaction was carried out by the addition of a small excess of triethylamine to a solution of equimolar quantities of the reagents in absolute ether. The stoichiometric equation for the formation of the quinone oxime-arenesulfenates can be written in the following form.

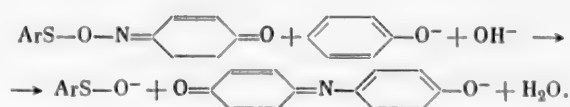


The quinone oxime-arenesulfenates are considerably less soluble in ether than the starting materials and therefore immediately precipitate. The reaction proceeds almost quantitatively. This method allows the final product to be rapidly isolated with no noticeable decomposition of the quinone oxime-arenesulfenates. The latter were freed of triethylamine hydrochloride by washing the precipitate rapidly on the filter with water. The moist product was rapidly dried in a stream of warm air and was recrystallized.

In the course of this work four representatives of the class of quinone oxime-arenesulfenates were obtained which are not described in the literature. The pure, crystalline quinone oxime-arenesulfenates are comparatively stable on storage and possess sharp melting points. Unrecrystallized 1,4-benzoquinone oxime-*o*-nitro-benzenesulfonate, which contained a considerable quantity of impurities, rapidly darkened in air.

By interaction with phenols in a basic medium the quinone oxime-arenesulfenates give a blue (violet) color. The reaction occurs rather rapidly in the cold. However, in a weakly basic medium, the rate of formation of the color is somewhat less than for the corresponding quinone oxime-arenesulfonates. This circumstance is obviously due to the cleavage of the less basic ions (corresponding to the stronger acid) from the nitrogen atom in the indophenol reaction of the quinone oxime-arylsulfonates.

The formation of the simplest indophenols (see the Table) as the products of the indophenol reaction was shown by paper chromatography. The formation of compounds of the indophenol-N-oxide type was not observed. Thus it was confirmed that the quinone oxime-arenesulfenates have the structure of O-esters. A yellow precipitate was formed during the indophenol reaction. Apparently this precipitate is a mixture of diaryldisulfide and arylarenethiosulfonate. The formation of the diaryldisulfide was shown during the indophenol reaction of 1,4-benzoquinone oxime-*o*-nitro-benzenesulfonate. It is possible that the primary products of the indophenol reaction are the unstable arenesulfenate ions according to the equation:



This proposal is in agreement with the work of Zincke, who described the isolation of diaryldisulfide from solutions containing arenesulfenate ions [6]. According to the data of this author, the mixture of diaryldisulfide and arylarenethiosulfonate is formed as a result of the basic hydrolysis of the esters of the arenesulfenic acids.

The hydrolysis of quinone oxime-arenesulfenates proceeds more slowly than the hydrolysis of the quinone oxime-arenecarboxylates. Thus quinone oxime-arenesulfenates, in contrast to the majority of quinone oxime-arenecarboxylates, show the indophenol reaction even after a brief treatment with a 10% solution of sodium hydroxide. The formation of the quinone oximes as a result of the basic hydrolysis of the quinone oxime-arenesulfenates under the conditions of the indophenol reaction was confirmed by paper chromatography (see the Table).

One ought to observe that esters of thymoquinone oxime with arenesulfenic acids are almost unreactive with the phenylate ion in the cold. This is an additional confirmation of the dependence of the indophenol reaction on the magnitude of the oxidation-reduction potential of the *p*-quinone, which corresponds to the given *N*-substituted *p*-quinoneimine. In contrast to thymoquinone oxime-arenesulfonates [1], thymoquinoneoxime-arenesulfenates do not give a blue color with phenols in a basic medium even on heating.

EXPERIMENTAL

1,4-Benzoquinone oxime-*o*-nitrobenzenesulfenate. In 100 ml of dry ether, free of alcohol, were dissolved 1.23 g of 1,4-benzoquinone oxime and 1.9 g of *S*-chloro-*o*-nitrothiophenol (*o*-nitrobenzenesulfonyl chloride). The solution was filtered to remove a small quantity of an insoluble substance. Triethylamine, 1.4 ml (about 0.01 mole), was added drop-wise to the filtrate, which was cooled to 0-5° and mechanically stirred. An orange, crystalline solid immediately began to precipitate. The mixture was stirred for an additional 5 min (on longer stirring the product darkened); the precipitate was filtered off, washed with water, and dried in a stream of warm air. The orange, crystalline product (m.p. 98-99°), which was obtained in practically quantitative yield, was immediately purified by recrystallization from *n*-hexane. Orange-red platelets, m.p. 109°. The substance was very soluble in acetone, benzene, and glacial acetic acid, somewhat less soluble in carbon tetrachloride, dioxane, and alcohol (better on heating); difficultly soluble in ether; insoluble in water. It colored the skin brown. When rapidly heated or when heated above the melting point it exploded. It gave a blue color with a basic solution of phenol even in the cold. A qualitative analysis demonstrated the presence of sulfur.

Found %: N 10.17. $\text{C}_{12}\text{H}_8\text{O}_4\text{N}_2\text{S}$. Calculated %: N 10.14.

The Chromatography of the Products of the Indophenol Reaction of Quinone Oxime-arenesulfenates

The no. of the experiment	The name of the ester	ArOH	The products of the reaction	The R _f values, the concentration of ammonia (in grams per liter)	
				10	30
1	-	-	Indophenol	0.59	0.59
2	-	-	Indophenol-N-oxide	0.49	0.51
3	-	-	1,4-Benzoquinone oxime	0.40	0.41
4	-	-	Naphthol-indophenol	0.94	0.95
5	1,4-Benzoquinone oxime- <u>o</u> -nitrobenzenesulfenate	Phenol	Indophenol 1,4-Benzoquinone oxime	0.59 0.40	0.60 0.41
6	1,4-Benzoquinone oxime- <u>o</u> -nitrobenzenesulfenate	α -Naphthol	Naphthol-indophenol 1,4-Benzoquinone oxime	0.94 0.41	0.95 0.42
7	1,4-Benzoquinone oxime-2,4-dinitrobenzenesulfenate	Phenol	Indophenol 1,4-Benzoquinone oxime	0.59 0.41	0.59 0.42
8	1,4-Benzoquinone oxime-2,4-dinitrobenzenesulfenate	α -Naphthol	Naphthol-indophenol 1,4-Benzoquinone oxime	0.94 0.40	0.96 0.41

2,5-Thymoquinone-2-oxime-o-nitrobenzenesulfenate. In 100 ml of dry ether, free of alcohol, were dissolved 1.79 g of 2,5-thymoquinone oxime-2 and 1.9 g of S-chloro-o-nitrothiophenol. To the solution at room temperature and with mechanical stirring was added drop-wise 1.4 ml of triethylamine. The precipitated orange solid was filtered off and washed on the filter with water until free of triethylamine hydrochloride. The product was then washed on the filter with small portions of ethyl alcohol. This caused almost all of the solid to dissolve. The alcohol filtrate was diluted with a large volume of water; the precipitated, yellow, flocculant solid was filtered off and dried at 40-50°. An additional quantity of the product was obtained by evaporation of the ethereal filtrate and purification of the substance which precipitated. The total yield was almost quantitative. The orange-yellow crystals (from n-octane) melted at 135°. The substance is quite soluble in the majority of organic solvents, but insoluble in water. With a basic solution of α -naphthol it gives a violet color. Qualitative analysis confirmed the presence of sulfur.

Found %: N 8.45. $C_{16}H_{16}O_4N_2S$. Calculated %: N 8.43.

1,4-benzoquinone oxime-2,4-dinitrobenzenesulfenate. This was obtained in analogous fashion to 1,4-benzoquinone oxime-o-nitrobenzenesulfenate by the addition of a small excess of triethylamine with solution of 1,4-benzoquinone oxime and 2,4-dinitrobenzenesulfonyl chloride in dry ether. The yield was almost quantitative. The product was isolated as golden-yellow needles from alcohol. M.p. 155°. It is quite soluble in acetone and glacial acetic acid; poorly soluble in benzene, carbon tetrachloride, and alcohol (better on heating); soluble with great difficulty in ether; insoluble in water. When heated strongly it explodes. With phenol in a basic medium it gives a blue coloration even in the cold. According to the qualitative analysis it contains sulfur.

Found %: N 13.20. $C_{12}H_7O_6N_3S$. Calculated %: N 13.08.

2,5-thymoquinone-2-oxime-2,4-dinitrobenzenesulfenate. This was obtained in analogous manner to 2,5-thymoquinone-2-oxime-o-nitrobenzenesulfenate by the addition of a small excess of triethylamine to a solution of 2,5-thymoquinone-oxime-2 and 2,4-dinitrobenzenesulfonyl chloride in dry ether. The yield (on the basis of the product obtained from the ethereal filtrate) was almost quantitative. Yellow needles from alcohol. M.p. 162.5°. A sample mixture with 2,5-thymoquinone oxime-2 showed a depression of the melting point of 22°. It is quite soluble in acetone, benzene, and glacial acetic acid, slightly soluble in alcohol (better on heating), difficultly soluble in n-octane and ether, insoluble in water. When heated strongly it explodes. With a basic solution of thymol it gives a green color in the cold; with α -naphthol a violet color is obtained. According to the qualitative analysis it contains sulfur.

Found %: N 11.11. $C_{16}H_{15}O_6N_3S$. Calculated %: N 11.14.

The isolation of the products of the indophenol reaction. An aliquot of finely divided 1,4-benzoquinone oxime-o-nitrobenzenesulfenate, recrystallized from n-octane, was added with thorough stirring to a solution of phenol taken in excess in 10% alkali. An intense color developed.* Stirring was continued for some time. The precipitate was filtered off, washed with a solution of phenol in alkali, and then with alcohol and dried. The orange-yellow substance thus obtained did not possess a sharp melting point but melted approximately at 150°.

When the indophenol reaction of 1,4-benzoquinone oxime-o-nitrobenzenesulfenate was carried out with phenol in alcoholic alkali medium with heating a more homogeneous product was obtained. A yellow crystalline substance was isolated from the solution on cooling; it melted at 186°. After washing with alcohol the melting point was raised to 189°. A sample mixture with o,o'-dinitrodiphenyldisulfide showed no depression of the melting point.

The chromatographing of the products of the indophenol reaction. Distributive chromatography on paper in a mixture of n-butyl alcohol and an aqueous solution of ammonia was used for the identification of the products obtained from the interaction of quinone oxime-arenesulfenates with basic phenol solutions. In addition to the blue (violet) stripes with relative distance movements characteristic of the salts of the simplest indophenols there were observed on the chromatograms some yellow stripes. The relative movement of these stripes corresponded to the values of the relative movements of salts of quinone oximes, which is confirmation that hydrolysis of the quinone oxime-arene-sulfenates occurs under the conditions of the indophenol reaction.

The relative movement factors cited in the table are given on the basis of three parallel experiments. The temperature during the chromatogramming was 20°.

SUMMARY

1. Four representatives of a so far unreported class of esters have been synthesized from quinone oximes and arenesulfenic acids.
2. Some properties of these compounds are described. The quinone oxime-arenesulfenates give colors with phenols in basic media (the indophenol reaction).
3. It was shown by distributive chromatography on paper that indophenols are obtained by this reaction and that splitting off of the arenesulfenyl residue occurs; hydrolysis simultaneously occurs with the formation of the quinone oximes.
4. The influence of some factors on the indophenol reaction was studied.

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* In these experiments the solution which was obtained after dissolving 1,4-benzoquinone oxime-o-nitrobenzenesulfenate was filtered to remove the small particles of some unreacted substance.

THE SYNTHESIS AND PROPERTIES OF ORGANOSILICON COMPLEX DIESTERS

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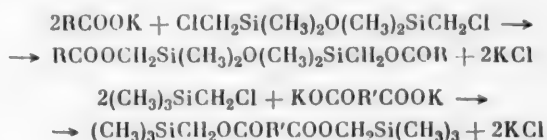
Original article submitted August 5, 1960

Complex organosilicon diesters – derivatives of organo-silicon alcohols and glycols (containing the siloxane bond in the molecule) have not been sufficiently studied. One might expect, however, that in analogy to organic complex diesters they could be interesting as model lubricating oils, plasticisers, etc.

The first of these diesters with the general formula $\text{RCOOCH}_2\text{Si}(\text{R}')_2\text{O}(\text{R}'')_2\text{SiCH}_2\text{OCOR}$, bis (acetoxymethyl) tetramethyldisiloxane was obtained by Speier and co-workers [1]. Derivatives of acrylic [2] and methacrylic [2-4] acids were later obtained, and also the acetates of various organosilicon glycols which contain complex ester groups in the α -, γ - and positions still further removed from the silicon atom [6,7]. Diesters have often been described which contain free carboxyl or hydroxyl end-groups; these were obtained by the interaction of acid salts of dibasic acids [8] or salts of hydroxy acids [9] with bis(halomethyl)tetraalkyldisiloxanes.

The syntheses of the diesters listed above were ordinarily accomplished by heating (sometimes in an autoclave) salts of acids with di(haloalkyl)tetraalkyldisiloxanes in solution in the corresponding acids or in polar solvents, for example – dimethylformamide. Organosilicon complex diesters of a similar type – derivatives of the higher aliphatic or aromatic acids – have not been obtained to this time. There are no data on organosilicon diesters of the second type $\text{R}_3\text{SiCH}_2\text{OCOR}'\text{COOCH}_2\text{SiR}_3$ either – derivatives of dibasic organic acids and organosilicon alcohols. These facts induced us to synthesize a series of diesters of these two types and to investigate some of their properties.

The reaction mentioned above between salts of acids and the halomethyl derivatives of alkylsilanes and siloxanes was used in these syntheses; the reaction proceeded easily on simple heating of the components in dimethylformamide, and the diesters were ordinarily obtained in yields of about 80%



The physical constants of the diester products are given in the Table.

In the syntheses of diesters of the second type there were noticeable differences apparent in the reactivity of the salts of the acids. This was shown by the different rates of increase of the boiling point of the reaction mixtures which contained two liquid components – dimethylformamide (b.p. 153°) and chloromethyltrimethylsilane (b.p. 97°). The rise of the boiling point of this mixture is connected with the changing composition of the liquid phase as the second, low boiling component of the mixture enters into the reaction, and the temperature rise thus appears as an indirect indicator of the rate at which the reaction is proceeding.

A comparison of the rates at which the boiling point of the reaction mixtures rose in different experiments showed that with the increase of the molecular weight of the dibasic acids the reactivity of their potassium salts strongly increased; this allowed the aliphatic acids which were investigated to be placed in the following order according to increasing activity; succinic < adipic < azelaic.

No. of Prod	The formula	The boiling point (pressure in mm)	The solidification point or melting	n_D^{20}	d_4^{20}	MRD	
						Found	Calc.
(I)	$[(CH_3CH_2COOCH_2Si(CH_3)_2)_2O]$	143° (4)	-29°	1.4255	0.9850	79.63	80.24
(II)	$[(CH_3)_2CHCOOCH_2Si(CH_3)_2)_2O]$	142 (2)	Below -71	1.4250	0.9632	88.80	89.50
(III)	$[C_6H_5COOCH_2Si(CH_3)_2)_2O]$	231 (2)	-45 (glass)	1.5115	1.0905	110.67	110.20
(IV)	$[(CH_3)_3SiCH_2OOCCH_2)_2]$	128 (1)	-23	1.4382	0.9548	79.90	80.49
(V)	$[(CH_3)_3SiCH_2OOCCH_2CH_2)_2]$	175-176 (5)	-26	1.4419	0.9497	88.74	89.75
(VI)	$[(CH_3)_3SiCH_2OOC(CH_2)_3)_2]$	218 (14)	-70 (glass)	1.4446	0.9325	102.85	103.64
(VII)	$[(CH_3)_3SiCH_2OOC(CH_2)_4)_2]$	201-202 (6)	-28	1.4443	0.9261	107.53	108.27
(VIII)	$[(CH_3)_3SiCH_2OOC]_2C_6H_4-o$	185 (7)	-	1.4973	1.0277	96.44	95.94
(IX)	$[(CH_3)_3SiCH_2OOC]_2C_6H_4-n$	-	115-116	-	-	-	-

From the determination of the solidification point of the diester products, the formation of supercooled solutions was noted in a number of cases; these later crystallized. The approximate crystallization temperatures for these compounds (IV, V and VII) were determined from the cooling curves.

The diesters of the dicarboxylic acids with an even number of carbon atoms (succinic, adipic and sebacic) crystallized on cooling, forming solid crystalline substances which were characterized by their very similar melting points (-23 to -28°). The diester of azelaic acid (with an odd number of carbon atoms) was converted at -70° to a transparent glass. Only the dipropionate of the diesters which contained siloxane bonds was able to crystallize at low temperatures. The dibenzoate was converted on cooling into a transparent glass, and the diisobutyrate remained mobile even at -70°.

EXPERIMENTAL

The starting materials. The salts of the mono- and dicarboxylic acids were obtained by the neutralization of an aqueous solution of potassium hydroxide with the calculated quantity of the organic acid; the salts were dried at 110°. Trimethylchloromethylsilane (X) was obtained by the photochemical chlorination of dimethyldichlorosilane with subsequent methylation of the methylchloromethyldichlorosilane with methyl magnesium bromide. Symmetrical bis(chloromethyl)tetramethyldisiloxane (XI) was obtained by the action of concentrated sulfuric acid on (X) [10].

Synthetic methods. A mixture of the organic acid salt and dry dimethylformamide (XII) was placed in a 500-ml round-bottomed flask with a tube, thermometer, mechanical stirrer, reflux condenser, and dropping funnel; the mixture was heated to boiling, and during 30-40 min with stirring there was added to it (X) or (XI). The reaction mixture was then boiled with stirring for various lengths of time, depending on the composition and structure of the components of the reaction. The mixture was cooled, the precipitated potassium chloride was filtered off, (XII) was distilled away, and the product of the reaction was fractionated *in vacuo*. When the reaction was carried out with the salts of dibasic acids and (X), the process was followed by the change of the boiling point of the reaction mixture. This temperature gradually rose from 121 (the boiling point of the starting mixture) to 153° [the boiling point of (XII)]

Symmetrical bis(propionoxymethyl)tetramethyldisiloxane (I). This was obtained by heating 60 g of (XI) and 75 g of potassium propionate in 160 g of (XII) for 6 hours. The yield was 60.4 g (77%).

Found %: Si 18.33; C 47.48; H 8.79. M 299. The ester number was 343. $C_{12}H_{26}O_5Si_2$. Calculated %: Si 18.33; C 47.02; H 8.55. M 306.4. The ester number was 366.

Symmetrical bis(isobutyroxymethyl)tetramethyldisiloxane (II). The synthesis was accomplished with 47.3 g of (XI), 60.9 g of sodium isobutyrate, and 150 g of (XII). After boiling for 2 hrs, there was isolated 54.9 g of (II). The yield was 81%.

Found %: Si 16.81; C 49.93; H 9.26. M 340. The ester number was 323. $C_{14}H_{30}O_5Si_2$. Calculated %: Si 16.79; C 50.26; H 9.04. M 334.5. The ester number was 335.4.

Symmetrical bis(benzooxymethyl)tetramethyldisiloxane (III). This was obtained from 66.2 g of (XI) and 95.6 g of potassium benzoate in 200 g of (XII). The mixture was boiled for 4 hours. There was obtained 98.3 g of (III). The yield was 81%.

Found %: Si 14.08; C 59.43; H 6.67. M 386; the ester number was 277. $C_{20}H_{28}O_6Si_2$. Calculated %: Si 13.95; C 59.66; H 6.51. M 402.6; the ester number was 278.7.

Bis(trimethylsilylmethyl)succinate (IV). This was obtained by boiling 61.3 g of (X) and 48.6 g of potassium succinate in 125 g of (XII) for 40 hours.

Found %: Si 19.69; C 49.55; H 9.32. M 305. Ester number 395. $C_{12}H_{26}O_4Si_2$. Calculated %: Si 19.33; C 49.51; H 9.02. M 290.5; ester number 386.3.

Bis(trimethylsilylmethyl)adipate (V). This was obtained from 42.6 g of (X) and 37.5 g of potassium adipate in 125 g of (XII). After 6 hrs of boiling there was isolated 42.9 g of (V). The yield was 78%.

Found %: Si 17.14; C 52.64; H 9.55. M 314. Ester number 365. $C_{14}H_{30}O_4Si_2$. Calculated %: Si 17.64; C 52.78; H 9.49. M 318.6; ester number 352.2

Bis(trimethylsilylmethyl)azelate (VI). This was obtained from 36.8 g of (X) and 39.6 g of potassium azelate by boiling for 3 hrs in 125 g of (XII). There was isolated 44.3 g of (VI). The yield was 82%.

Found %: Si 15.24; C 56.63; H 10.10. M 358; ester number 310. $C_{17}H_{36}O_4Si_2$. Calculated %: Si 15.60; C 56.66; H 10.07. M 360.6; ester number 311.

Bis(trimethylsilylmethyl)sebacate (VII). This was obtained from 36.8 g of (X) and 41.8 g of potassium sebacate in 125 g of (XII) by boiling for 30 hrs. The yield of (VII) was 34.8 g (59.5%). *

Found %: Si 14.80; C 58.51; H 10.48. M 376; ester number 297. $C_{19}H_{38}O_4Si_2$. Calculated %: Si 15.00; C 57.70; H 10.22. M 374.7; ester number 299.5.

Bis(trimethylsilylmethyl)phthalate (VIII). A mixture of 49.1 g of (X) and 48.5 g of potassium phthalate was boiled for 5 hrs in 125 g of (XII). There was isolated 40.5 g of (VIII). ** The yield was 60%.

Found %: Si 14.88; C 58.48; H 7.94. $C_{16}H_{26}O_4Si_2$. Calculated %: Si 16.60; C 56.76; H 7.74.

Bis(trimethylsilylmethyl)terephthalate (IX). This was obtained after 25 hrs of boiling from 49.1 g of (X) and 48.5 g of potassium terephthalate in 300 g of (XII). The solid precipitate on the filter was washed many times with water and was recrystallized from alcohol. Thin transparent light platelets were obtained. M.p. 115-116°. The yield of (IX) was 68.7%.

Found %: Si 17.11; C 56.61; H 7.97. M 337; ester number 333. $C_{16}H_{26}O_4Si_2$, calculated %: Si 16.60; C 56.76; H 7.74. M 338.5; ester number 331.5.

The melting and solidification points of the diesters were determined in the usual manner. The approximate crystallization temperatures of the esters which crystallized at low temperatures were taken from the cooling curves. The ester numbers were determined by hydrolysis of the diesters with solutions of alkali in diethylene glycol. The elementary analyses were carried out by the microanalytical group under the direction of Yu. N. Platonova.

SUMMARY

We synthesized 9 new organosilicon complex diesters and investigated some of their properties. It was shown that the reactivity of the potassium salt of the dibasic organic acids in the reaction with trimethylchloromethylsilane increases with the increase of the molecular weight of the acid.

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*The extent of the reaction and the lowered yield of (VII) can be explained by the fact that the potassium salt of the acid contained potassium hydroxide as an impurity.

**The diester isolated, judging from the analytical data, contained an impurity from which it could not be freed.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

REACTIONS OF PHOSPHINES

I. REACTIONS OF PRIMARY ALIPHATIC PHOSPHINES WITH ALDEHYDES AND KETONES

K. A. Petrov and V. A. Parshina

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Phosphines, contrary to amines, have been little studied up to now. This is explained by the fact that phosphines, especially primary and secondary ones, are difficultly-accessible substances. At the same time phosphines, as well as other compounds of trivalent phosphorus, being highly reactive, may be used for syntheses of various substances. The transition from phosphines to other phosphorus compounds is usually accomplished through mobile hydrogen atoms or the free electron pair of the coordinatively-unsaturated phosphorus atom. However, the corresponding reactions have been little used in the synthesis of organophosphorus compounds.

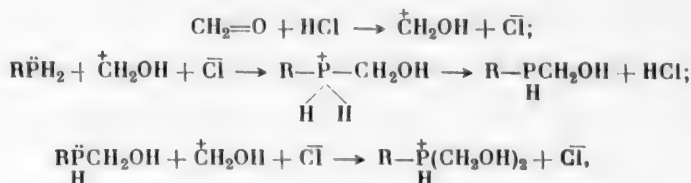
Reactions of primary aliphatic phosphines with aldehydes and ketones were studied in the present work. These reactions had not been studied earlier, although analogous reactions of phosphine with aldehydes and ketones are known, and their products are used to prepare substances of high molecular weight [1-4].

We showed that primary aliphatic phosphines readily react with formaldehyde in the presence of hydrochloric acid to form alkyltrimethylolphosphonium chlorides.



The mechanism of this reaction apparently consists in alternating processes of addition of a carbenium cation to phosphorus and splitting-out of hydrogen chloride from the intermediate phosphonium.

The end product is an alkyltrimethylolphosphonium chloride. The reaction may be expressed by the following schemes:



This reaction gives good yields of quaternary phosphonium chlorides; a better yield (84.3%) is obtained when the reaction is carried out at 20° with ratios of the phosphine, hydrochloric acid, and formaldehyde, equal to 1:1:3.5, respectively. The yield is appreciably decreased if the reaction is carried out at a temperature lower or higher than the optimum.

The reaction considered has a general character in the sense that primary phosphines readily react with various aldehydes and ketones. The reaction sometimes stops at the first or second degree of alkylation of the phosphine; this depends on the solvent and the character of the aldehyde or ketone taking part in the reaction. For instance, propylphosphine reacts with benzaldehyde in the presence of hydrochloric acid in aqueous-alcoholic solution to form propyltri(phenylmethylol)phosphonium chloride, whereas in absolute ether solution in the presence of hydrogen chloride it reacts to form propyldi(phenylmethylol)phosphine. However, propylphosphine reacts with acetophenone in dry ether solution under the same conditions to form only a secondary phosphine - propyl (α-phenylethylol)phosphine. This is connected with the electrophilic character of the methylol groups in the phosphines under consideration, the basicity of the solvent, and probably, in the last case, steric peculiarities which hinder the addition of a second ketone molecule to the phosphine.

EXPERIMENTAL

1. Propyltrimethylolphosphonium chloride. To 54 ml of 34% formaldehyde and 21 ml of 33% hydrochloric acid, 15 g of propylphosphine was added at 20° in a current of nitrogen during 30 min, with stirring. The reaction mass was kept, with continual stirring, at 40-50° for 2-3 hr and left to stand at room temperature for 10-12 hr. Then the water was removed in vacuo at a temperature not over 75°. There was obtained 33.5 g of a thick, colorless oil (yield 84.3%, reckoned on the propylphosphine taken). The substance was soluble in water, alcohol, and acetic acid. The oil was purified by dissolving it in anhydrous methanol, adding animal charcoal, shaking, and then removing the solvent from the filtrate.

n_D^{20} 1.5280, d_4^{20} 1.2554. Found %: C 35.35; H 7.84; Cl 17.31; P 15.16. $C_8H_{16}O_3PCl$. Calculated %: C 35.56; H 7.95; P 15.29; Cl 17.49.

2. Propyltriethylolphosphonium chloride was prepared under conditions similar to those described above. From 5 ml of acetaldehyde, 3 ml of 34% hydrochloric acid, and 1.5 g of propylphosphine in 10 ml of aqueous methanol, 4.1 g of a thick, crystallizing oil was obtained (yield 85%). The substance was soluble in water, acetic acid, and alcohol.

Found %: P 12.58; Cl 14.39. $C_9H_{22}O_3PCl$. Calculated %: P 12.66; Cl 14.49.

The same results were obtained when hydrogen chloride was passed into a solution of acetaldehyde and propylphosphine in absolute ether.

3. Propyltri(phenylmethyl)phosphonium chloride was prepared under conditions similar to those described in paragraph 1. From 15 ml of benzaldehyde, 7 ml of 34% hydrochloric acid, and 4 g of propylphosphine in 25 ml of methanol, 17 g (75%) of a thick oil was obtained. The substance was soluble in water and alcohol.

Found %: P 6.91, 7.24; Cl 8.47. $C_{24}H_{28}O_3PCl$. Calculated %: P 7.19; Cl 8.22.

4. Propyldi(phenylmethyl)phosphine. Hydrogen chloride was passed for 15 min through 1.5 g of propylphosphine and 4 ml of benzaldehyde in 5 ml of absolute ether; then the reaction mass was kept at 40° for 30 min. After removing the solvent in vacuo the resulting oil was purified by dissolving it in anhydrous methanol, adding animal charcoal, and shaking. The oil, obtained after distilling the solvent from the filtrate, crystallized on long standing. M.p. 174-175°. The substance was soluble in alcohol and benzene.

Found %: P 11.40, 11.58. $C_{17}H_{21}O_2P$. Calculated %: P 10.74.

5. Propyl(α -phenylethyl)phosphine was prepared under conditions similar to those described in paragraph 1. From 20 ml of acetophenone, 7 ml of hydrochloric acid (d 1.17), and 4 g of propylphosphine in 20 ml of methanol, 2.5 g of a thick oil was obtained. The substance was soluble in alcohol and benzene. The product obtained, decomposed on distillation in vacuo.

Found %: P 15.48. $C_{11}H_{17}OP$. Calculated %: P 15.79.

SUMMARY

The reactions of propylphosphine with formaldehyde, acetaldehyde, benzaldehyde, and acetophenone were studied; it was shown that in the presence of hydrochloric acid substituted phosphonium salts and phosphines are formed in this case.

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STUDY OF THE CHEMICAL PROPERTIES OF THE ACID DIESTER OF METHYLPHOSPHONOUS ACID AND ETHYLENE GLYCOL

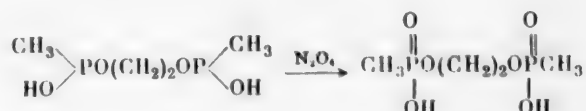
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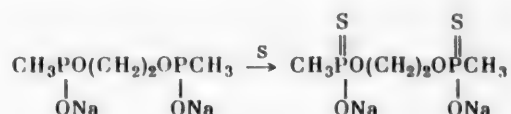
Original article submitted July 22, 1960

Earlier we showed that acid bismethylphosphonites are readily formed by transesterification of monoethyl methylphosphonite with glycols [1]. In the present work certain chemical conversions of the simplest bisphosphonite, synthesized on transesterification with ethylene glycol, were studied. The new types of organophosphorus compounds obtained, contain two phosphonic groupings interconnected by a chain of atoms.

Oxidation of the bisphosphonite with nitrogen oxides [2] gave a nearly-quantitative yield of the bisphosphonate, whose structure was confirmed by analytical and potentiometric-titration data.

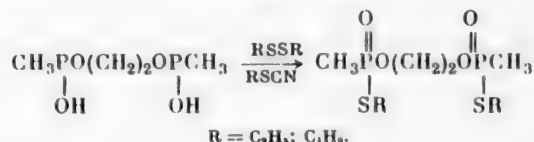


The synthesized acid is dibasic (the observed titration equivalent agreed with the calculated value). The acid bisphosphonate is strongly hygroscopic, being converted by moisture to the hydrate. It is well known that acid phosphites and phosphonites add on sulfur to form the corresponding thioacids [3,4]. It was found that when a mixture of the bisphosphonite and sulfur is heated, the bistiophosphonate is formed; however, it cannot be isolated from the reaction mixture owing to the formation of admixtures difficult to separate. The pure product cannot be isolated even when the reaction is carried out in a dioxane medium. However, if the reaction is carried out with the sodium salt of the acid, sulfur addition takes place readily, since the sodium derivatives of the phosphonites are fixed tervalent forms.



The sodium salt is isolated in the form of an oil which crystallizes on standing; it is easiest to isolate the substance in the form of the bisbenzylisothiuronium salt.

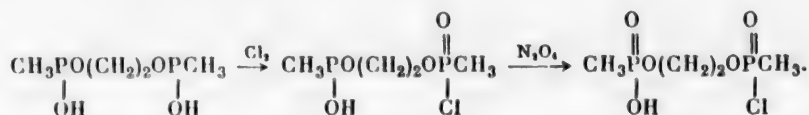
We recently showed that the acid bisphosphonite reacts with diethyl disulfide [1]. In the present work we studied both this reaction and the synthesis of dithiophosphonates based on alkyl thiocyanates.



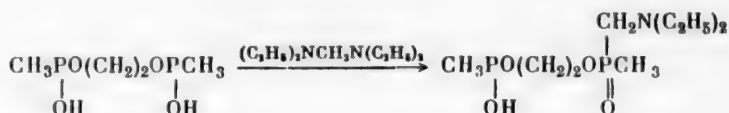
*The sodium derivative of the original acid bisphosphonite is obtained when the phosphonite reacts with sodium methoxide in an anhydrous methanol medium. If necessary, the sodium derivative may be isolated in pure form.

We were unable to prepare bisdithiolphosphonates through the reaction of the original phosphonite with sulfonyl chlorides.

Unexpected results were obtained on chlorination of acid bisphosphonites. Treatment with sulfuryl chloride did not lead to the desired product; treatment with chlorine gave the monochloride, which was converted to the corresponding acid by oxidation with nitrogen oxides.



Like other acid esters of tervalent phosphorus, the bisphosphonite being studied is aminomethylated [5] on treatment with diaminomethylenes. When the bisphosphonite reacts with tetraethyldiaminomethylene in the molar ratio 1 : 1 the "monomethyldiethylaminophosphonate" is formed.



The resulting substance forms a methiodide and gives a test for tervalent phosphorus, which proves its structure.

Thus the studied acid bisphosphonite may be used to synthesize various polyfunctional organophosphorus compounds. It should be noted that the reactivities of the two phosphonite groups in this compound are different, owing to which only one of them reacts in some cases.

EXPERIMENTAL

Oxidation of Ethylene Bismethylphosphonite. Four g of the acid bisphosphonite was put into a flask protected from atmospheric moisture, and a mixture of dry nitrogen and nitrogen oxides was passed through it, the flask being cooled with snow and salt. When the oxidation was finished (the mixture acquired a stable, blue-green color), the excess nitrogen oxides were removed by bubbling dry nitrogen through the mixture at atmospheric pressure and in vacuo. There was obtained 4.5 g (98%) of ethylene acid methylphosphonate.

n_D^{20} 1.4635, d_4^{20} 1.4220, M_{RD} 42.10; cal. 42.17; equiv. 110, cal. 109. Found %: P 26.14; 26.05. $\text{C}_4\text{H}_{12}\text{O}_6\text{P}_2 \cdot \text{H}_2\text{O}$. Calculated %: P 26.22.

The product was a thick, odorless liquid readily soluble in water and alcohol and insoluble in ether, benzene, carbon tetrachloride, and chloroform.

Addition of Sulfur to Ethylene Bismethylphosphonite Sodium Salt. To a solution of 1.15 g of sodium in 15 ml of anhydrous methanol, 4.65 g of the acid bismethylphosphonite in 10 ml of anhydrous methanol was added; then the mixture was stirred for 1 hr at 40-50°, 1.6 g of sulfur added in portions, and the mixture stirred for 2 hr more at 50-60°. After evaporation of the alcohol the thick mass was kept in vacuo at 100°. There was obtained 7 g (95%) of an oily product which crystallized on long standing; the substance was washed with methanol and dried in a vacuum desiccator; m. p. 101-103.5°.

Found %: C 15.87, 15.96; H 3.41, 3.09. $\text{C}_4\text{H}_{10}\text{O}_4\text{P}_2\text{S}_2\text{Na}_2$. Calculated %: C 16.31; H 3.40.

The bisbenzylisothiuronium salt was obtained by mixing aqueous solutions of the prepared salt and benzylisothiuronium chloride; m. p. 101-103.5° (from a benzene-acetone mixture).

Found %: N 10.49, 10.51. $\text{C}_{12}\text{H}_{22}\text{O}_4\text{N}_4\text{S}_4\text{P}_2$. Calculated %: N 10.18.

Chlorination of Ethylene Bismethylphosphonite. Dry chlorine was passed through a mixture, cooled to 5-10°, of ethylene bismethylphosphonite and 20 ml of anhydrous carbon tetrachloride until a stable coloration appeared. The solvent was evaporated in a water-jet pump vacuum, and the residue was kept at 60-70° in vacuo (1 mm) for 2 hr. There was obtained 5.5 g (nearly-quantitative yield) of the monochloride.

n_D^{20} 1.4855, d_4^{20} 1.4610, MR_D 43.39; cal. 44.40. Found %: Cl 16.0, 16.1. $C_4H_{11}O_4P_2Cl$. Calculated %: Cl 16.16.

The product was a thick, yellow liquid soluble in alcohol, dioxane, and tetrahydrofuran and insoluble in ether, benzene and carbon tetrachloride. It gave a test for trivalent phosphorus; on oxidation with nitrogen oxides, as described above, it gave ethylene acid methylphosphonate methylchlorophosphinate in nearly-quantitative yield.

n_D^{20} 1.4790, d_4^{20} 1.4850, MR_D 45.32; cal. 45.89. Found %: P 26.65, 26.16; Cl 14.95, 14.50. $C_4H_{11}O_5P_2Cl$. Calculated %: P 26.20; Cl 15.05.

The product was a thick, yellow liquid soluble in alcohol and dioxane and insoluble in ether, benzene, and carbon tetrachloride; it did not give a test for trivalent phosphorus.

Reaction of Ethylene Bismethylphosphonite. a) With Dibutyl Disulfide. An 8.36 g quantity of the bismethylphosphonite, 20 g of dibutyl disulfide, and a small piece of sodium were heated *in vacuo* to 110-115°; in this case butyl mercaptan distilled off. After 4 hr the mixture temperature had risen to 140-145°, and 85-95% of the theoretical amount of butyl mercaptan must have been driven off; the remaining material was distilled in a high vacuum. All operation had to be carried out in a dry nitrogen atmosphere. There was obtained 5.4 g (33%) of *o*, *o*-ethylene S, S-dibutyl bismethylthiolphosphonate.

B.p. 104-105° (10⁻⁴ mm), n_D^{20} 1.5009, d_4^{20} 1.1570, MR_D 92.1; cal. 92.16. Found %: P 17.01, 17.21; S 17.62, 17.51. $C_{12}H_{28}O_4P_2S_2$. Calculated %: P 17.09; S 17.69.

The product was a thick, yellow liquid with a disagreeable odor, soluble in alcohol and dioxane and insoluble in ether and toluene.

b) With Methyl Thiocyanate.* A 9.3 g quantity of the bismethylphosphonite and 13 g of methyl thiocyanate were heated at 110° for 6 hr (3.5 ml of hydrocyanic acid must have condensed in the cooled receiver). After distillation in high vacuum there was obtained 3.5 g (25.2%) of *o*, *o*-ethylene S, S-dimethyl bismethylthiolphosphonate.

B.p. 84-85° (10⁻⁴ mm) n_D^{20} 1.5072, d_4^{20} 1.2750, MR_D 65.03; cal. 64.50. Found %: P 21.96; 21.69; S 22.61, 22.27. $C_4H_{16}O_4P_2S_2$. Calculated %: P 22.24; S 22.96.

The product was a thick, colorless liquid with a disagreeable odor, soluble in alcohol and dioxane and insoluble in ether and benzene.

c) With Tetraethyldiaminomethylene. A 9.3 g quantity of the bismethylphosphonite and 7.9 g of tetraethyldiaminomethylene were heated for 6 hr at 120-130° (2.8 g of diethylamine must have condensed in the receiver). After distillation in high vacuum two fractions were obtained: the 1st, b.p. up to 96° (10⁻⁴ mm), and the 2nd b.p. 96-105° (10⁻⁴ mm). Crystals separated from the 2nd fraction on standing; they were filtered out, and washed with cold petroleum ether. The yield of the diaminomethylation product was 0.3 g; m.p. 94-95.5° (in a sealed capillary).

Found %: P 17.49, 17.96; N 7.68, 7.54. $C_{14}H_{34}O_4N_2P_2$. Calculated %: P 17.45; N 7.86.

The filtrate was redistilled; 6.7 g (50%) of the monoaminomethylation product was obtained.

B.p. 98-99° (10⁻⁴ mm) n_D^{20} 1.4742, d_4^{20} 1.1360, MR_D 67.01; cal. 67.31. Found %: N 5.41, 5.37. $C_9H_{23}O_4NP_2$. Calculated %: N 5.16.

The product was a colorless liquid soluble in water and ether. It formed a methiodide which crystallized on long standing; m. p. 43-45° (after washing with an ether petroleum ether mixture).

Found %: N 3.53, 3.69. $C_{10}H_{26}O_4NP_2I$. Calculated %: N 3.39.

SUMMARY

1. A convenient method for oxidizing ethylene bismethylphosphonite to the corresponding bisphosphonate has been found.

2. The addition of sulfur to the bismethylphosphonite sodium salt was studied.

3. It was shown that the bisphosphonite reacts with disulfides and thiocyanates to form the corresponding dithiol derivatives.

*In carrying out the given synthesis all precautions, necessary in work with hydrocyanic acid, had to be taken.

4. Chlorination of the bismethylphosphonite takes place only at one phosphorus atom.
5. The aminomethylation of the bismethylphosphonite was studied.

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X • ON BY-PRODUCTS OF THE REFORMATSKII REACTION

G. S. Grinenko, V. I. Maksimov and V. I. Aksenova

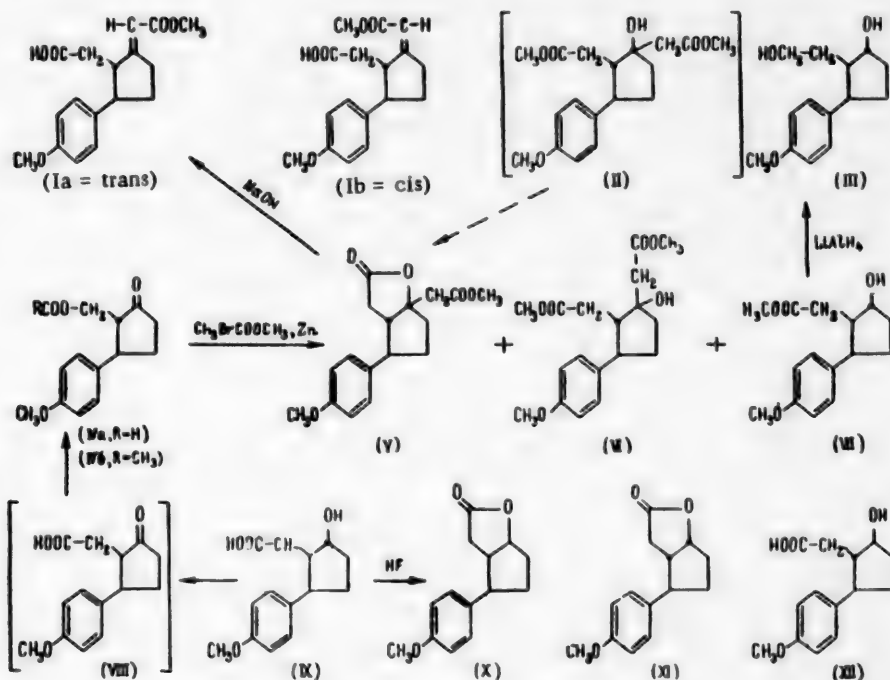
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Original article submitted July 28, 1960.

The condensation of methyl *trans*-3-(*p*-methoxyphenyl) cyclopentanone-1-acetate-2 [1] (IVb) with methyl bromoacetate under the conditions of the Reformatskii reaction leads to the formation of a mixture of two epimeric hydroxy esters (II) and (VI), of which isomer (II), having hydroxyl and carbomethoxymethyl in the *cis*-arrangement, is converted to lactone (V) in the course of the reaction. The Reformatskii reaction is not stereospecific and, as a rule, leads to a mixture of isomers [2,3]. Moreover, a by-product of the reaction – methyl *anti*-*cis*-3-(*p*-methoxyphenyl) cyclopentanol-1-acetate-2 (VII) – was isolated.

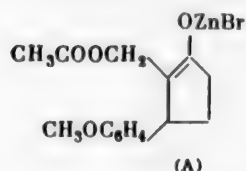
These substances were separated by chromatographing on alumina. After treatment with 1 mole-equiv. of methanolic sodium hydroxide solution, lactone (V) was converted by β -elimination to unsaturated acid (Ia). The exocyclic position of the double bond in acid (Ia) was confirmed by the UV spectrum, which contains two maxima at 226 and 275 m μ , characteristic of the secondary-tertiary α, β -unsaturated ester and anisole groupings. Only one isomer of the acid was obtained; this obviously had the *trans*-configuration (Ia), since the formation of the *cis*-compound (Ib) involves the overcoming of substantial steric hindrance. The stereoselectivity of lactone conversion to an unsaturated acid was shown by Linstead [4] in the case of monomethyl *trans*- Δ^3 -dihydromuconate.



*For article IX see ZhOKh 30, 574 (1960).

Hydroxy esters (VI) and (VII) cannot be completely separated by chromatographing on alumina, since these substances have nearly the same polarity; Hydroxy ester (VI) is isolated from the first fractions and hydroxy ester (VII), from the last ones. Hydrolysis of the last fractions, containing hydroxy ester (VII) gives hydroxy acid (IX).

The by-product of the Reformatskii reaction – hydroxy ester (VII) – is a product of the reduction and isomerization of the original keto ester (IVb). In the literature there are data indicating that the keto group is reduced during the Reformatskii reaction [5]. It is of interest that the stable *trans*-isomer (IVb) gives the less-stable *cis*-isomer (VII). The formation of anti-*cis*-hydroxy ester (VII) from *trans*-keto ester (IVb) may be represented as proceeding through the formation of zinc bromoenolate (A).



Three of the four theoretically possible isomers of 3-(*p*-methoxy-phenyl)cyclopentanol-1-acetic-2 acid, (X), (XI), and (XII), two of which exist in the form of lactones (X) and (XI), were prepared earlier [1]. The configuration of the fourth isomer of hydroxy ester (VII), described in the present article, was proved by converting it to the known *syn-cis*-lactone (X) by treatment with anhydrous hydrogen fluoride [1]. Oxidation of hydroxy acid (IX) with sodium bichromate in acetic acid [6] gave not the expected *cis*-keto acid (VIII) but the *trans*-acid (IVa), since isomerization took place during the reaction, the stable *trans*-isomer being formed.

In order to prepare methyl *trans*-2-carboxymethyl-3-(*p*-methoxy-phenyl)cyclopentylideneacetate-1 (Ia) – an intermediate in the synthesis of steroid-hormone analogs – the crude Reformatskii-reaction product was treated, without chromatographic separation, with an equivalent quantity of methanolic sodium hydroxide solution. In this case acid (Ia) was obtained in 35-39% yield, reckoned on keto ester (IVb).

EXPERIMENTAL

Methyl *trans*-3-(*p*-Methoxyphenyl)cyclopentanone-1-acetate-2 (IVb) [1]. To a suspension of 15 g of *trans*-3-(*p*-methoxyphenyl)cyclopentanone-1-acetic-2 acid (Ia) and 30 g of anhydrous potash in 150 ml of dry acetone and 150 ml of dry methanol, 30 ml of methyl iodide was added. The reaction mass was stirred for 15 hr at room temperature. The potassium iodide and excess potash were filtered out, and the mother liquor was evaporated *in vacuo*. An ethereal solution of the residue was washed with water, dried, and the ether distilled off. Yield 13.95 g (88%), m.p. 39-41°.

Reformatskii Reaction. A mixture of 21.5 g (0.082 mole) of methyl *trans*-3-(*p*-methoxyphenyl)cyclopentanone-1-acetate-2, 22.6 ml (0.246 mole) of methyl bromoacetate, 29 g (0.45 mole) of activated zinc, and 0.72 g (0.0049 mole) of iodine was boiled, and simultaneously stirred with a Hershberg stirrer, for 6 hours in a dry nitrogen atmosphere. The methyl bromoacetate was added in three equal portions (~7.5 ml) during 2 hr. After cooling the reaction mass with ice water, cold, dilute acetic acid was added to it. The benzene-ether solution was separated, washed with water, dilute ammonia solution (3-4 times), and finally saturated sodium chloride solution, and dried. After distilling off the solvent there was obtained 28.31 g of a colored oil, which was dissolved in 100 ml of benzene and chromatographed on 280 g of alumina.

a) A 7.4 g quantity of *syn-trans*-1-carbomethoxymethyl-3-(*p*-methoxyphenyl)cyclopentanol-1-acetic-2 lactone in the form of an oil, was eluted with benzene. The IR spectrum contained bands for CO-1734 cm⁻¹. A 7.4 g quantity of the oil was dissolved in 200 ml of methanol, and 26.3 ml of 1 N sodium hydroxide was added. The reaction mass was boiled for 3 hr and then evaporated *in vacuo*. An aqueous solution of the residue was extracted with ether and acidified with 5% hydrochloric acid solution. The resulting precipitate was filtered out, washed with water, and dried. There was obtained 5.46 g (24%) of methyl *trans*-3-(*p*-methoxyphenyl)-2-carboxymethylcyclopentylidene-acetate-1 in the form of a colorless precipitate with m.p. 125-126° (from a 1:1 benzene-ether mixture).

UV spectrum: λ_{\max} 226 m μ , $\log \epsilon$ 4.42 and λ_{\max} 275 m μ , $\log \epsilon$ 3.53.

Found%: C 67.19; H 6.78. M 307 (by titration). C₁₇H₂₀O₅. Calculated%: C 67.09; H 6.62. M 304.33.

b) Nine fractions were eluted with a methanol-ether mixture (1:20). Each fraction was evaporated *in vacuo*, and the residues were dissolved in an ether-petroleum ether mixture and left to stand in a refrigerator. The precipitate, which formed in fractions 1-4, was filtered out. There was obtained 0.71 g of anti-*trans*-1,2-carbomethoxymethyl-3-(*p*-methoxyphenyl)cyclopentanol-1, m.p. 59.5-60°.

The IR spectrum contained the absorption bands; OH 3470 cm^{-1} and CO 1732, 1706 cm^{-1} .

Found %: C 64.20; H 7.13. $\text{C}_{18}\text{H}_{24}\text{O}_6$. Calculated %: C 64.46; H 7.19.

A precipitate of methyl anti-cis-3-(p-methoxyphenyl)cyclopentanol-1-acetate-2, m.p. 43-44°, was isolated from the last fractions. It gave a melting-point depression with 1,2-carbomethoxymethyl-3-(p-methoxyphenyl)-cyclopentanol-1.

The IR spectrum contained the absorption bands: CO 1736 cm^{-1} and OH 3470 cm^{-1} .

Found %: C 68.07; H 7.72. $\text{C}_{18}\text{H}_{26}\text{O}_4$. Calculated %: C 68.16; H 7.62.

After hydrolysis of fractions 5-9 with methanolic sodium hydroxide solution there was obtained 3.3 g (14.5%) of anti-trans-3-(p-methoxyphenyl)cyclopentanol-1-acetic-2 acid, m.p. 135-135.5° (from water, charcoal being used).

Found %: C 67.04; H 6.74. M 250 (by titration). $\text{C}_{14}\text{H}_{18}\text{O}_4$. Calculated %: C 67.18; H 7.25. M 250.28.

Methyl syn-trans-3-(p-methoxyphenyl)-2-carboxymethylcyclopentylideneacetate-1 (Ia). A mixture of 29.3 g of methyl trans-3-(p-methoxyphenyl)cyclopentanone-1-acetate-2, 36 ml of methyl bromoacetate, 40 g of activated zinc, and 2 g of iodine was boiled, with stirring, in a dry nitrogen atmosphere for 6 hr.

After decomposition there was obtained 34.37 g of an oil; it was dissolved in 1000 ml of methanol, 113 ml of 1 N sodium hydroxide added, and the mixture boiled for 3 hr and then evaporated *in vacuo*. An aqueous solution of the residue was extracted with ether and acidified with 5% hydrochloric acid solution, and the precipitate was filtered out, washed with water, and dried. Yield 12.45 g (36.6%), m. p. 121.5-123°.

Syn-cis-3-(p-methoxyphenyl)cyclopentanol-1-acetic-2 lactone (X). A solution of 0.3 g of anti-cis-3-(p-methoxyphenyl)cyclopentanol-1-acetic-2 acid in 10 ml of anhydrous hydrogen fluoride in a Teflon vessel was left to stand for 3 hr at room temperature. The hydrogen fluoride was removed with a current of air, the residue dissolved in ether and the ethereal solution washed with water, bicarbonate solution, and again water. Yield 0.14 g, m.p. 69-69.5° (from alcohol). The resulting lactone did not give a melting point depression with the lactone prepared earlier [1].

Found %: C 71.99; H 6.90. $\text{C}_{14}\text{H}_{16}\text{O}_3$. Calculated %: C 72.40; H 6.94.

Anti-cis-3-(p-Methoxyphenyl)cyclopentanol-1- β -ethanol-2 (III). A solution of 0.39 g of methyl anti-cis-3-(p-methoxyphenyl)cyclopentanol-1-acetate-2 in 15 ml of dry ether was added dropwise to a suspension of 0.1 g of lithium aluminum hydride in 10 ml of dry ether at such a rate that the reaction mass boiled. Then it was heated to boiling for 1 hr more and cautiously decomposed with water. The ethereal solution was washed with water, dried, and the solvent distilled off. Yield 0.25 g, m.p. 72.5-74°.

The IR spectrum contained the absorption bands OH 3300 and 3280 cm^{-1} .

Found %: C 71.38; H 8.38. $\text{C}_{14}\text{H}_{20}\text{O}_3$. Calculated %: C 71.15; H 8.53.

Oxidation of anti-cis-3-(p-Methoxyphenyl)cyclopentanol-1-acetic-2 acid. A solution of 0.5 g of anti-cis-3-(p-methoxyphenyl)cyclopentanol-1-acetic-2 acid in 5.5 ml of acetic acid and 5.5 ml of benzene was added dropwise in a current of nitrogen, with stirring and cooling, to a solution of 0.21 g of sodium bichromate in 2.5 ml of acetic acid. The reaction mass was stirred for 48 hr at room temperature. Then it was poured into 160 ml of water and extracted with ether. The ethereal extract was washed with water, sodium bicarbonate solution, and again water. There was obtained 0.3 g of trans-3-(p-methoxyphenyl)cyclopentanone-1-acetic-2 acid, m.p. 105-107°. It did not give a melting-point depression with a sample prepared earlier [1].

SUMMARY

In the condensation of methyl trans-3-(p-methoxyphenyl)cyclopentanone-1-acetate-2 with methyl bromoacetate under the conditions of the Reformatskii reaction, the normal course of the process, with the formation of syn-trans-1-carbomethoxymethyl-3-(p-methoxyphenyl)cyclopentanol-1-acetic-2 acid and anti-trans-1, 2-carbomethoxymethyl-3-(p-methoxyphenyl)cyclopentanol-1, is accompanied by the reduction and isomerization of the original compound with the formation of methyl anti-cis-3-(p-methoxyphenyl)cyclopentanol-1-acetate-2.

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SUBSTITUTED ARYLAMIDES OF DITHIOCARBOXYLIC ACIDS

II. SYNTHESIS OF HALO-, SULFO-, AND CARBOXY-N-PHENYLDITHIOOXAMIDES

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The synthesis of alkoxy-N-phenyldithiooxamides was described in the preceding article [1]. It is well known that the introduction of halogens into the molecules causes the appearance or enhancement of physiological activity in the compounds [2]. On this basis it was of interest to synthesize and to study the properties of halo-, sulfo-, and carboxy-substituted dithiooxanilamides (Table 1), on which there are no data in the literature.

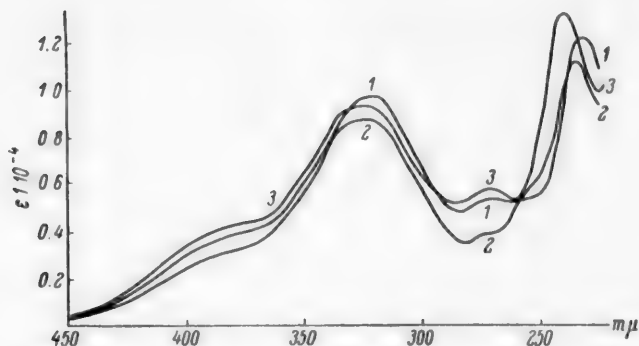


Fig. 1. Ultraviolet absorption spectra of substituted dithiooxanilamides. 1) Dithiooxanilamide; 2) *o*-chlorodithiooxanilamide; 3) *p*-chlorodithiooxanilamide.

Substituted dithiooxanilamides were prepared by reducing the corresponding thiooxanilonitriles with hydrogen sulfide in an alcoholic-aqueous medium saturated beforehand with ammonia gas. Toward the end of saturation with hydrogen sulfide an orange-red, crystalline precipitate formed, which was purified by crystallization from alcohol.

Absorption curves for *ortho*- and *para*-chloro-substituted dithiooxanilamides are shown in Fig. 1.

The original thiooxanilonitriles (Table 2) were prepared in good yield through the interaction of the corresponding phenyl mustard oils and acetone cyanhydrin in an alkaline, alcoholic-aqueous medium [1].

The phenyl mustard oils in turn were prepared from aromatic amines and thiophosgene in a hydrochloric acid medium [3].

Absorption curves for chloro-substituted thiooxanilonitriles are shown in Fig. 2.

As is evident from Fig. 2, the absorption maxima of *ortho*-chloro-substituted thiooxanilonitriles are shifted toward the short-wave region of the spectrum in comparison with the absorption maxima of the corresponding *para*-chloro-substituted ones.

EXPERIMENTAL

***p*-Sulfothiooxanilonitrile Sodium Salt.** To 20 g of *p*-sulfophenyl isothiocyanate sodium salt in 50 ml of alcohol 10 ml of acetone cyanhydrin and 5 g of sodium hydroxide dissolved in 25 ml of water were added. When the alkali was added, the mustard oil quickly dissolved and the solution darkened.

On the next day 6 ml of glacial acetic acid was added to the solution. The resulting orange precipitate was filtered out, and washed with 25 ml of alcohol. Yield 11.1 g (50%). An additional 10 g of product was isolated from the filtrate by evaporation *in vacuo*. The nitrile was purified by crystallization from dilute alcohol.

***o*-Chlorothiooxanilonitrile.** To 5 g of *o*-chlorophenyl isothiocyanate in 30 ml of alcohol, 4 ml of acetone cyanhydrin and 1.5 g of sodium hydroxide dissolved in 15 ml of water were added. The mixture was shaken periodically until the mustard oil, which separated from the alcoholic solution on addition of the aqueous alkali, had completely

TABLE 2. Thiooxanilonitriles



R	Molecular formula	M	Color	Yield (in %)	Melting point	% N		% S	
						Found	Calc.	Found	Calc.
o-Cl	$\text{C}_8\text{H}_5\text{N}_2\text{SCl}$	196.5	Brown	94	107°	13.92, 14.02	14.24	—	—
o-Br	$\text{C}_8\text{H}_5\text{N}_2\text{SBr}$	241	Same	87	101	11.37, 11.40	11.62	—	—
o-I	$\text{C}_8\text{H}_5\text{N}_2\text{SI}$	288	Deep-yellow	87	79	9.71, 9.75	9.72	—	—
p-Cl	$\text{C}_8\text{H}_5\text{N}_2\text{SCl}$	196.5	Yellow	90	120—122	13.97, 14.04	14.24	—	—
p-Br	$\text{C}_8\text{H}_5\text{N}_2\text{SBr}$	241	Same	95	127	10.98, 10.95	11.62	—	—
p-I	$\text{C}_8\text{H}_5\text{N}_2\text{SI}$	288	"	90	151	9.38, 9.30	9.72	—	—
p-NH ₂ SO ₂	$\text{C}_9\text{H}_5\text{N}_2\text{O}_3\text{S}_2\text{Na}$	264	"	50	—	8.60, 8.61	10.60	—	—
p-COOH,	$\text{C}_9\text{H}_6\text{O}_2\text{N}_2\text{S}$	206	"	97	179—181	13.11, 13.20	13.59	15.61, 15.54	15.53
p-C ₆ H ₅ COOC	$\text{C}_{11}\text{H}_{10}\text{O}_2\text{N}_2\text{S}$	234	"	91	182	11.84, 11.85	11.96	—	—
p-COOH, <i>m</i> -OH	$\text{C}_9\text{H}_6\text{O}_3\text{N}_2\text{S}$	222	"	96	195	12.28, 12.49	12.61	—	—

TABLE 1. Dithiooxanilamides



R	Molecular formula	M	Color	Yield (in %)	Melting Point	% N		% S	
						Found	Calc.	Found	Calc.
<i>o</i> -Cl	C ₈ H ₇ N ₂ S ₂ Cl	230.5	Red	21	154–155°	11.73, 11.89	12.14	—	—
<i>o</i> -Br	C ₈ H ₇ N ₂ S ₂ Br	275	Orange	40	176	9.93, 9.93	10.18	—	—
<i>o</i> -I	C ₈ H ₇ N ₂ S ₂ I	322	Same	45	186	8.54, 8.50	8.69	19.65, 19.82	19.87
<i>p</i> -Cl	C ₈ H ₇ N ₂ S ₂ Cl	230.5	"	34	178.5	12.21, 11.90	12.14	27.78, 27.62	27.76
<i>p</i> -Br	C ₈ H ₇ N ₂ S ₂ Br	275	"	26	180	10.17, 10.28	10.18	—	—
<i>p</i> -I	C ₈ H ₇ N ₂ S ₂ I	322	"	27	179–180	8.53, 8.50	8.69	—	—
<i>p</i> -NH ₂ SO ₂	C ₈ H ₉ O ₂ N ₃ S ₃	275	Silver-gray	23	—	15.59, 15.73	15.27	—	—
<i>p</i> -NaOSO ₂	C ₈ H ₇ O ₃ N ₂ S ₂ Na	298	Light-yellow	34	—	9.65, 9.76	9.39	32.36, 32.33	32.21
<i>p</i> -COOH, <i>m</i> -OH	C ₉ H ₆ O ₃ N ₂ S ₂	256	Light-brown	46	—	10.72, 10.86	10.93	—	—
<i>p</i> -COOH(H ₂ O)	C ₉ H ₁₀ O ₃ N ₂ S ₂	240	"	14	205	10.98, 10.78	10.86	24.37, 24.51	24.77

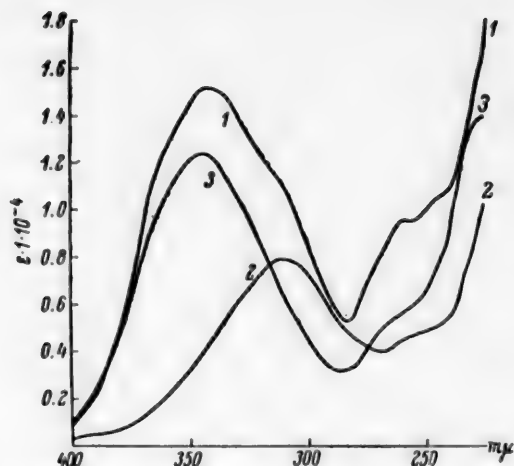


Fig. 2. Absorption spectra of substituted thiooxanilonitriles. 1) Thiooxanilonitrile; 2) *o*-chloro-thiooxanilonitrile; 3) *p*-chlorothiooxanilonitrile.

dissolved. On the next day the solution was filtered, diluted with twice its volume of water, and neutralized with hydrochloric acid until an acid reaction was obtained. The resulting precipitate was filtered out, washed with water, and dried. Yield 5.5 g brown crystals.

The substituted thiooxanilonitriles listed in Table 2 were prepared under similar conditions.

***p*-Sulfodithiooxanilamide Sodium Salt.** Three g of *p*-sulfothiooxanilonitrile sodium salt was mixed with 10 ml of alcohol, and ammonia was passed through the mixture until the nitrile dissolved completely. Hydrogen sulfide was then passed into the solution until an orange precipitate formed. The precipitate was filtered out, washed with alcohol, and dried. Yield 1.3 g (35%). The product was recrystallized from dilute alcohol.

In some experiments the *p*-sulfodithiooxanilamide sodium salt was prepared directly from the mustard oil without isolating the intermediate nitrile. In this case the solution, obtained after the reaction of *p*-sulfophenyl isothiocyanate with acetone cyanhydrin, was saturated successively with ammonia and hydrogen sulfide. The substituted dithiooxanilamides, listed in Table 1, were prepared under similar conditions.

SUMMARY

Ten new substituted thiooxanilonitriles and the corresponding substituted dithiooxanilamides were synthesized. The absorption spectra of some of them were measured.

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FLUOROMETHYL ESTERS OF SULFURIC ACID

V. INTERACTION OF FLUOROMETHYL ETHERS AND SULFURIC ANHYDRIDE

G. A. Sokol'skii and M. A. Dmitriev

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The preparation of difluorodimethyl sulfate through the reaction of sulfuric anhydride with difluorodimethyl ether was reported earlier [1]. It was found that this reaction can be used to prepare other fluorine-containing sulfates. Attempts to prepare trifluoro- and tetrafluorodimethyl sulfates by this method are considered in the present article.

The trifluoro- and tetrafluorodimethyl ethers, required for this purpose, were prepared through the exchange reaction of halogens in the corresponding chloro-substituted ethers, prepared in turn by chlorinating 1,2-dichlorodimethyl ether. It should be noted that the description, given in the literature [2], of the reaction of trichlorodimethyl ether with antimony trifluoride is insufficiently accurate and, despite repeated attempts, was not fully reproducible. The recommended method of preparing trifluoro- and difluorochlorodimethyl ethers, which consists in refluxing a mixture of trichlorodimethyl ether with sublimed antimony trifluoride, was found to result in considerable decomposition of the final products owing to their reaction with the glass of the apparatus (formaldehyde, carbon monoxide, hydrogen chloride, and hydrogen fluoride are evolved). The decomposition is autocatalytic in character; owing to this the above-mentioned fluoroethers could not be obtained sufficiently pure and in the indicated yield. Considerably better results were achieved by using a reaction vessel which was inert to hydrogen fluoride, and adding a catalyst - antimony pentachloride. Really good yields of trifluoro- and difluorochlorodimethyl ethers are obtained by this method.*

TABLE 1

Formula	Boiling point	d_4^{20}	n_D^{20}	$M R_D$	
				Found	Calc.
$\text{CHCl}_2\text{—O—CH}_2\text{Cl}$	130—131°	1.5036	1.4734	27.90	27.68
$\text{CHF}_2\text{—O—CH}_2\text{Cl}$	55—56	1.3682	1.3401	17.85	17.73
$\text{CHF}_2\text{—O—CH}_2\text{F}$	29—30	1.3294	1.270	13.1	12.99
$\text{CHCl}_2\text{—O—CHCl}_2$	144—145	1.6565	1.5015	32.73	32.55
CHFCl—O—CHCl_2	98—99	1.5321	1.4302	28.23	27.53
$\text{CHF}_2\text{—O—CHCl}_2$	57—58	1.4610	1.3666	23.17	22.59
$\text{CHF}_2\text{—O—CHFCl}$	28—29	1.3852 (−70°)	1.290	17.6	17.86
$\text{CHF}_2\text{—O—CHF}_2$	+2	1.43	—	—	—

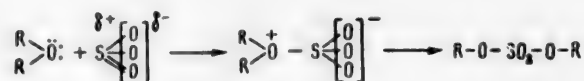
The indicated method was used to carry out the exchange reaction of the halogens in symmetrical tetrachlorodimethyl ether. It was found that when this ether reacts with sublimed antimony trifluoride in the presence of antimony pentachloride, all products of stepwise halogen exchange are formed.** When the reaction is carried out by heating the reaction mixture at atmospheric pressure, the main product is difluorodichlorodimethyl ether; when the mixture is heated in an autoclave at 120°, the main product is tetrafluorodimethyl ether. Certain properties of the fluoro-substituted ethers obtained, are compared with the properties of the original chloro-substituted ethers in Table 1.

*1,1,2-Trifluorodimethyl ether, prepared earlier [2], was erroneously assigned the structure of the 1,1,1-trifluoro derivative.

**In a patent [3], dealing with the reaction of tetrachlorodimethyl ether with antimony trifluoride, the only isolated product reported is an unknown substance with b.p. 61°, which is described as if it were trifluorochlorodimethyl ether with m.p. (−130) (−115°).

The fluoro-substituted dimethyl ethers, prepared by the indicated method, were caused to react with sulfuric anhydride; in this case it was found that the ease with which this reaction goes, depends on the number of halogen atoms in the ether molecule. Thus while dimethyl ether reacts vigorously with sulfuric anhydride at a temperature well below 0° [4] and methyl difluoromethyl ether reacts vigorously at about -20° [1], trifluorodimethyl ether reacts on heating to 40-50°, and tetrafluorodimethyl ether reacts only on heating for many hours in an autoclave at 70-80°; hexafluorodimethyl ether* is inert to sulfuric anhydride even at 150-180°.

The observations given, confirm the hypothesis, advanced earlier [6], on the mechanism of interaction of ethers with sulfuric anhydride, namely, that in the first stage of this reaction a bipolar ion is formed by filling the octet of the sulfur atom in the polarized sulfuric anhydride molecule with an unshared electron pair of the ether oxygen; subsequently an alkyl group in the bipolar ion migrates to an oxygen atom in the sulfur trioxide part of the molecule and forms a dialkyl sulfate.



No doubt the more electrodotic the ether is, the more readily the first stage of the reaction takes place. On the other hand, when substituents with a negative inductive effect (e.g., a halogen atom) are introduced in the α -position of the alkyl radical, the ether becomes less electrodotic, and its reaction with sulfuric anhydride is correspondingly hindered. When halogen atoms accumulate in the α -position of the ether, it becomes still less electrodotic. In the case of fully-halogenated ethers the electron density in the oxygen atom obviously is diminished to the maximum degree, and such ethers cannot react with sulfuric anhydride despite the extremely pronounced electrophilic character of the latter.

On studying the interaction of fluorine-containing ethers and sulfuric anhydride it was also found that the nature of the reaction products is determined to a considerable degree by the thermal instability of the fluorinated sulfates formed. This factor is of transcendent importance, since the original reagents interact, as was indicated above, only under certain temperature conditions. Thus the reaction of 1,1,2-trifluorodimethyl ether with sulfuric anhydride, both without solvent and in chloroform or carbon tetrachloride solution, which takes place at 40-50°, is accompanied by the evolution of carbon monoxide, hydrogen fluoride, and paraformaldehyde; no fluorosulfates can be isolated.

Symmetrical tetrafluorodimethyl ether was caused to react with sulfuric anhydride by heating a mixture of the reagents in an autoclave at 70° for many hours. As in the preceding case, a large amount of gaseous decomposition products (carbon monoxide and hydrogen fluoride) is formed in the reaction; the main reaction product is difluoromethyl fluorosulfonate, formed in 70% yield, which is identical with the compound obtained earlier in the electrochemical fluorination of methyl chlorosulfonate [7]. The formation of difluoromethyl fluorosulfonate in the reaction of tetrafluorodimethyl ether with sulfuric anhydride, is probably preceded by that of symmetrical tetrafluorodimethyl sulfate, which decomposes on heating, evolving carbon monoxide and hydrogen fluoride.

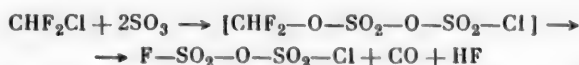


The given scheme is confirmed by the fact that when tetrafluorodimethyl sulfate, prepared from methyl difluoromethyl sulfate [1], is heated to 70°, quantitative formation of difluoromethyl fluorosulfonate actually occurs.

The results of the thermal decomposition of difluoromethyl fluorosulfonate are additional confirmation of the reaction mechanism considered above. When this compound is heated in an autoclave above 120°, hydrogen fluoride, sulfur fluoride, and carbon monoxide are formed.



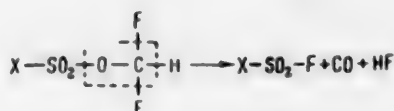
The formation of pyrosulfuryl fluorochloride in the reaction of difluorochloromethane with sulfuric anhydride, is explained by a similar scheme.



* In the present work we used hexafluorodimethyl ether obtained as a by-product of the electrochemical fluorination of dimethyl sulfate [5].

This reaction is carried out by heating the reaction mixture in an autoclave at 85-90° for many hours.

The observations given, indicate that compounds, containing a difluoromethoxyl group bound to a sulfonyl, are thermally unstable and tend to decompose in a direction common to substances of a great diversity of types.



EXPERIMENTAL

1. Reaction of Trichlorodimethyl Ether with Antimony Trifluoride. A mixture of 30.0 g of trichlorodimethyl ether, 42.0 g of sublimed antimony trifluoride, and 4.5 g of antimony pentachloride was put into a steel reaction vessel provided with an efficient reflux condenser, and heated in a boiling water bath for 2 hr. When the reaction mixture had cooled, the reflux condenser was disconnected, and the low-boiling components distilled off by heating the mixture to 150°. The collected distillate, amounting to 22.5 g, was fractionated, the following fractions being isolated:

1) b.p. 25-31°, 9.1 g (45.3%), trifluorodimethyl ether; 2) b.p. 31-52°, 1.6 g; 3) b.p. 52-58°, 6.5 g (27.8%), difluorochlorodimethyl ether; 4) b.p. 58-90°, 1.7 g; 5) b.p. 90-95°, 2.5 g; residue (dark-brown liquid) 1.3 g.

The results of analyses of the compounds obtained are given in Table 2.

TABLE 2.

Formula	Found (%)					Calculated (%)				
	C	H	F	Cl	M	C	H	F	Cl	M
C ₂ H ₃ OF ₂ Cl	20.90	2.84	33.00	29.32	—	20.63	2.58	32.64	30.52	—
C ₂ H ₃ OF ₃	23.82	2.72	56.50	—	102.6	24.00	3.00	57.00	—	100.0
C ₂ H ₃ OF ₄	20.18	1.88	64.00	—	119.5	20.33	1.69	64.40	—	118.0
C ₂ H ₂ OF ₃ Cl	18.06	1.69	42.02	26.71	136.3	17.86	1.49	42.35	26.40	134.5
C ₂ H ₂ OF ₂ Cl ₂	16.16	—	25.52	46.78	—	15.91	—	25.18	47.02	—
C ₂ H ₂ OFCl ₃	14.01	—	11.64	63.85	—	14.34	—	11.35	63.60	—

2. Reaction of Tetrachlorodimethyl Ether with Antimony Trifluoride. a) Similarly treated, 30.0 g of tetrachlorodimethyl ether, 44.5 g of antimony trifluoride, and 4.5 g of antimony pentachloride gave 24.4 g of a distillate, which was fractionated, the following fractions being isolated:

1) b.p. 45-60°, 14.1 g (52.3%), difluorodichlorodimethyl ether; 2) b.p. 60-95°, 1.3 g; 3) b.p. 95-101°, 6.3 g (23%), fluorotrichlorodimethyl ether; residue (dark-brown liquid) 2.7 g.

b) A mixture of 30.0 g of tetrachlorodimethyl ether, 44.5 g of sublimed antimony trifluoride, and 4.5 g of antimony pentachloride was heated in a steel autoclave at 120° for 8 hr. After cooling, the autoclave was opened and the low-boiling components were distilled off by heating to 150°, being condensed in an ice-salt mixture. The collected distillate, amounting to 20.6 g, was fractionated, the following fractions being isolated:

1) b.p. 0-3°, 9.8 g (50.9%), tetrafluorodimethyl ether; 2) b.p. 3-25°, 0.9 g; 3) b.p. 25-31°, 4.2 g (19.2%), trifluorochlorodimethyl ether; 4) b.p. 31-55°, 1.1 g; 5) 55-60°, 3.2 g (13%), difluorodichlorodimethyl ether; 6) b.p. 60-85°, 1.4 g; residue (dark-brown liquid) 0.3 g.

The results of analyses of the compounds obtained are given in Table 2.

3. Reaction of Tetrafluorodimethyl Ether with Sulfuric Anhydride. A mixture of 12.0 g of tetrafluorodimethyl ether and 8.0 g of freshly-distilled sulfuric anhydride was heated in a steel autoclave at 60-70° for 8 hr. After cooling the autoclave the gaseous products were released, and collected in a gasometer over water. The liquid residue was

kept cold with an ice-salt mixture, and 6 g of potassium fluoride was added to it in small portions with stirring, after which the low-boiling components were distilled off by heating to 100°. The collected distillate, amounting to 11.8 g (78.8%), was fractionated; it proved to be difluoromethyl fluorosulfonate, b.p. 34-34.5°; d_4^{20} 1.5668 and n_D^{20} 1.299 [7].

The gas collected in the gasometer, amounting to about 2 liters, proved to be carbon monoxide palladous chloride test.

Found: M 28.5.CO. Calculated: M 28.0.

4. Thermal Decomposition of Tetrafluorodimethyl Sulfate. A 9.9 g quantity of tetrafluorodimethyl sulfate was heated in a steel autoclave at 70° for 2 hr. After cooling, 7.05 g (94%) of difluoromethyl fluorosulfonate and about 1 liter of carbon monoxide were isolated from the reaction mixture.

5. Thermal Decomposition of Difluoromethyl Fluorosulfonate. Five g of difluoromethyl fluorosulfonate was heated in a steel autoclave at 120° for 4 hr. Then the autoclave was connected to a system, consisting successively of a casing filled with 5 g of potassium fluoride, a trap cooled with an acetone-carbon dioxide mixture, a wash bottle containing an alcoholic ethoxide solution, and a gasometer. After cooling the autoclave the gaseous reaction products were slowly released; the increase in weight of the casing containing potassium fluoride was 0.6 g; the amount of condensate in the trap was 3.1 g; about 0.6 liter of gas was collected in the gasometer.

The condensate was distilled, and proved to be sulfuryl fluoride, m.p. (-59)-(-57°).

Found %: F 37.80 (argentometry through lead fluorochloride after dissolving a weighed sample in ethoxide solution) M 100.5. O_2F_2S . Calculated %: F 37.25. M 102.0.

The gas, collected in the gasometer, proved to be carbon monoxide palladous chloride test.

Found %: M 29.0.CO. Calculated: M 28.0.

The walls of the autoclave were found to be coated with a dark-brown, resinous deposit (about 0.5 g).

6. Reaction of Difluorochloromethane with Sulfuric Anhydride. A mixture of 16.0 g of freshly-distilled sulfuric anhydride and 9.0 g of difluorochloromethane was heated in a steel autoclave at 85-90° for 20 hr. After cooling the autoclave the gaseous components were released, and collected in a gasometer over water. The liquid residue was fractionated in a steel apparatus. Yield 16.4 g (82.6%) - pyrosulfuryl fluorochloride:

B.p. 99.5-100°; d_4^{20} 1.7934, n_D^{20} 1.3946. Found %: F 9.52; Cl 17.59; S 31.86. M 203.4 O_6S_2FCl . Calculated %: F 9.57; Cl 17.87; S 32.28. M 198.5. Literature data [8]; b.p. 100.1°, d_4^{20} 1.797.

The gas collected in the gasometer, amounting to about 2.1 liters, proved to be carbon monoxide.

SUMMARY

1. The reaction of tetrafluorodimethyl ether with sulfuric anhydride was studied.
2. The thermal decomposition of tetrafluorodimethyl sulfate and difluoromethyl fluorosulfonate was studied.
3. The reaction of difluorochloromethane with sulfuric anhydride was studied, and pyrosulfuryl fluorochloride was prepared.
4. The general character of the direction of thermal decomposition of difluoromethyl esters of sulfuric acid and some of its derivatives, was brought out.

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AMIDES OF AROMATIC SULFONIC ACIDS

II. MIXED DIARYLSULFONAMIDES AND THEIR HYDROLYSIS

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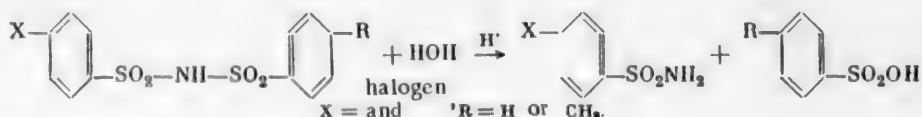
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Continuing an investigation in the field of secondary aromatic sulfonic acid amides [1], we synthesized a number of mixed diarylsulfonamides through the interaction of arylsulfonamides and arylsulfonyl chlorides in an aqueous-alkaline medium, and studied the conditions of their reverse conversion to sulfonic acids by hydrolysis.

It was found that symmetrical and mixed diarylsulfonamides are stable to hydrolysis of the S-N bond in the presence of caustic alkalis even on heating to 250°. However, they are hydrolyzed by 70% sulfuric acid even at 170°, and arylsulfonamide and an arylsulfonic acid being formed; in the case of monohalodiarylsulfonamides the sulfonamido group remains on the halogen-containing nucleus.



When the temperature is raised to 240° (which is done by increasing the sulfuric acid concentration to 85%), the hydrolysis of diarylsulfonamides goes further - to arylsulfonic acids:



The stability of diarylsulfonamides to hydrolysis of the S-N bond in caustic alkali solutions, thus brought out, provides grounds for assuming that the halogen atoms of halodiarylsulfonamides can be replaced by hydroxyl groups, analogously to their replacement by amino groups [2], by heating the amides with caustic alkalis in the presence of catalysts. The results of this investigation will be reported in a future article.

EXPERIMENTAL

Fifteen mixed diarylsulfonamides, synthesized by us by the method described earlier [1], are characterized in the table given below. They all are white, crystalline substances slightly soluble in cold water, readily soluble in alcohol (on heating), acetone, and pyridine, and practically insoluble in ether and aromatic hydrocarbons. Like symmetrical compounds of this series, mixed diarylsulfonamides develop acid properties in aqueous solutions, displacing carbonic acid from its salts.

Hydrolysis of Diarylsulfonamides by Sulfuric Acid. A 33.15 g quantity of *p*-monochlorodibenzene-sulfonamide and 75 ml of 70% sulfuric acid were boiled for 30 min (170° in the mixture), cooled to room temperature, poured into 100 g of crushed ice, and filtered. The precipitate was washed in the filter with 45-50 ml of ice water, well squeezed out, and recrystallized from water (1:30). There was obtained 14-15 g of *p*-chlorobenzenesulfonamide, m.p. 143-144°.

The mother liquor was neutralized with chalk, the gypsum precipitate filtered out, and the filtrate evaporated to 1/3 of its initial volume, acidified (to Congo) with concentrated sulfuric acid, and left for 1-2 days for crystallization. The resulting crystals were filtered out, washed with ice water, and dried; there was obtained 9-10 g of a substance whose properties corresponded to those described in the literature for benzenesulfonic acid [3].

Conditions of Synthesis and Results of Analyses of Mixed Diarylsulfonamides.

Amide	Original substance	Reaction temp.	Yield of amide in %	Conditions of crystallization	Melting point	Found (%)			Molecular formula	Calculated (%)		
						C	H	N		C	H	N
p-Monofluorodibenzene-sulfonamide	p-Fluoro-BSA* and BSC*	50—55°	60—62	W **, 1:20	140—141°	45.59	3.23	4.47	C ₁₂ H ₁₀ O ₄ NS ₂ F	45.70	3.19	4.44
p-Monochlorodibenzene-sulfonamide	p-Chloro-BSA and BSC	50—55	78—80	W 1:30	176.5—177.5	43.32	3.10	4.16	C ₁₂ H ₁₀ O ₄ NS ₂ Cl	43.48	3.01	4.22
p-Monobromodibenzene-sulfonamide	p-Bromo-BSA and BSC	50—55	84—85	Alc. **, 1:5	182—183	38.26	2.71	3.79	C ₁₂ H ₁₀ O ₄ NS ₂ Br	38.33	2.68	3.72
p-Moniododibenzene-sulfonamide	p-Iodo-BSA and BSC	50—55	89—90	Alc. 1:15	201—202	33.89	2.40	3.35	C ₁₂ H ₁₀ O ₄ NS ₂ I	34.01	2.38	3.30
p-Fluoro-p'-chlorodibenzene-sulfonamide	p-Fluoro-BSA and p-chloro-BSC	55—60	68—70	Alc. 1:20	154—155	41.00	2.60	3.97	C ₁₂ H ₉ O ₄ NS ₂ FCI	41.20	2.59	4.00
p-Fluoro-p'-bromodibenzene-sulfonamide	p-Fluoro-BSA and BSC	55—60	70—72	Alc. 1:20	148—149	36.50	2.31	3.51	C ₁₂ H ₉ O ₄ NS ₂ FBr	36.55	2.30	3.55
p-Fluoro-p'-iododibenzene-sulfonamide	p-Fluoro-BSA and p-iodo-BSC	55—60	85—86	Alc. 1:20	139—140	32.59	2.07	3.20	C ₁₂ H ₉ O ₄ NS ₂ FI	32.64	2.05	3.17
p-Chloro-p'-bromodibenzene-sulfonamide	p-Bromo-BSA and p-chloro-BSC	55—60	74—75	Alc. 1:15	208—208.5	35.01	2.23	3.44	C ₁₂ H ₉ O ₄ NS ₂ ClBr	35.09	2.21	3.41
p-Chloro-p'-iododibenzene-sulfonamide	p-Iodo-BSA and p-chloro-BSC	55—60	78—80	Alc. 1:20	211—212	31.44	2.00	3.08	C ₁₂ H ₉ O ₄ NS ₂ ClI	31.49	1.98	3.06
p-Bromo-p'-iododibenzene-sulfonamide	p-Iodo-BSA and p-bromo-BSC	75—78	~90	Alc. 1:25	233.5—234	28.66	1.84	2.81	C ₁₂ H ₉ O ₄ NS ₂ BrI	28.70	1.81	2.78
p-Monomethylidibenzene-sulfonamide	p-Methyl-BSA and BSC	50—55	66—68	W 1:15	166—167	50.11	4.21	4.47	C ₁₃ H ₁₃ O ₄ NS ₂	50.14	4.20	4.50
p-Methyl-p'-fluorodibenzene-sulfonamide	p-Fluoro-BSA and p-methyl-BSC	70—75	74—75	W 1:15	138—139	46.80	3.65	4.27	C ₁₃ H ₁₂ O ₄ NS ₂ F	46.79	3.67	4.25
p-Methyl-p'-chlorodibenzene-sulfonamide	p-Chloro-BSA and p-methyl-BSC	70—75	78—80	W 1:20	158—158.5	45.11	3.52	4.07	C ₁₃ H ₁₂ O ₄ NS ₂ Cl	45.14	3.49	4.05
p-Methyl-p'-bromodibenzene-sulfonamide	p-Bromo-BSA and p-methyl-BSC	70—75	83—85	Alc. 1:15	178—179	40.08	3.06	3.60	C ₁₃ H ₁₂ O ₄ NS ₂ Br	40.00	3.09	3.58
p-Methyl-p'-iododibenzene-sulfonamide	p-Iodo-BSA and p-methyl-BSC	70—75	~90	Alc. 1:20	189—190	35.78	2.73	3.24	C ₁₃ H ₁₂ O ₄ NS ₂ I	35.74	2.76	3.23

*BSA - benzenesulfonamide; BSC - benzenesulfonyl chloride.

**W. - water; Alc. - alcohol.

Similarly 34.6 g of p-methyl-p'-chlorodibenzenesulfonamide gave 10-12 g of p-chlorobenzenesulfonamide and 6-7 g of p-toluenesulfonic acid [4], whereas 36.6 g of p,p'-dichlorodibenzenesulfonamide gave 13-14 g of p-chlorobenzenesulfonamide and 8-10 g of p-chlorobenzenesulfonic acid [5].

A solution of 36.6 g of p,p'-dichlorodibenzenesulfonamide in 75 ml of 85% sulfuric acid was boiled for 2 hr (240° in the mixture), cooled to room temperature, and poured into 100 g of ice. The precipitate formed was filtered out, washed with ice water, and recrystallized from water. There was obtained 15-16g of p-chlorobenzenesulfonic acid [5].

SUMMARY

1. For the first time derivatives of dibenzenesulfonamide were synthesized and characterized, which contain a methyl group or a fluorine, chlorine, bromine, or iodine atom in the para-position of one of the benzene nuclei, and also mixed derivatives of the stated amide, which contain either a methyl group in the para-position of one nucleus and a halogen in that of the other, or different halogen atoms in the para-positions of both nuclei.

2. It was found that when mixed diarylsulfonamides are boiled with 70% sulfuric acid at 170°, they are hydrolyzed, and arylsulfonic acid and an arylsulfonamide being formed; the sulfonamido group remains on the halogen-containing nucleus. When the sulfuric acid concentration is increased to 85% and the temperature raised to 240°, the hydrolysis of diarylsulfonamides gives arylsulfonic acids.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

N-SUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLINES

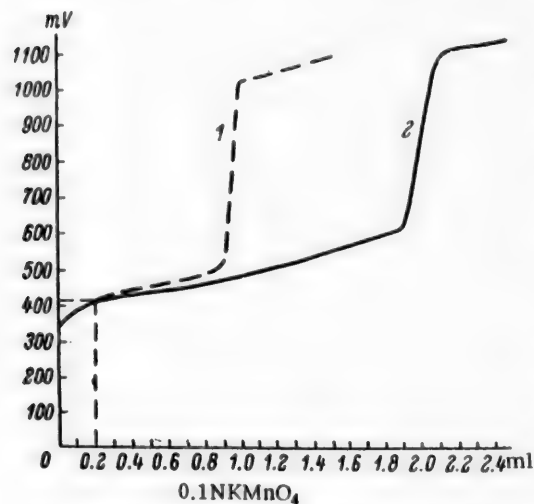
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Recently the attention of research workers has been attracted to 1,2,3,4-tetrahydroquinoline and its derivatives as antioxidants [1], repellents [2], insectofungicides [3], antiparasitic [4] and pharmacological agents for various purposes [5].

We synthesized a series of N-substituted tetrahydroquinolines, which were subjected to pharmacological tests and studied as repellents and fat antioxidants. The 1,2,3,4-tetrahydroquinoline used as starting material was obtained in a high yield by hydrogenating quinoline in an alcoholic solution in the presence of a nickel skeletal catalyst at 80-90° and a pressure of four to five atmospheres [6]. The conditions were studied for condensing tetrahydroquinoline with three-membered heterocyclic compounds: ethylene oxide, ethylene sulfide, and ethylenimine. It was shown that the condensation of tetrahydroquinoline with ethylene oxide takes place exothermally in the presence of traces of water and that products are formed by the addition of one, two, or three molecules of ethylene oxide.



Titration curves with potassium permanganate.
1) 0.01 M FeSO_4 ; 2) 0.01 M FeSO_4 + $1 \cdot 10^{-5}$ M
N-(β -cyanoethyl)-tetrahydroquinoline.

The nitrile to N-(γ -aminopropyl)-tetrahydroquinoline was effected using a nickel-aluminum alloy in an alkaline medium, and by saponification of the nitrile with alcoholic alkali the corresponding acid was obtained.

Acyl derivatives were synthesized by condensing several acyl halides with tetrahydroquinoline, and thiocarbamates were obtained by reaction with hydrogen sulfide in an alkaline medium [8]. The properties of the resulting tetrahydroquinoline derivatives are presented in the table.

Tetrahydroquinoline is a weak base, and its salts may be titrated quantitatively by a potentiometric method. Irreversible oxidation potentials, determined at 20° by the permanganate method [9], were found to be about 410-430 mV (Figure) for all N-substituted tetrahydroquinolines, and the oxidation equivalent is 12. From the latter it may be assumed that under these experimental conditions the pyridine ring is oxidized to oxalic acid and traces of anthranilic acid, as was shown previously [10].

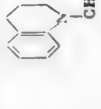
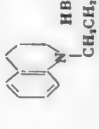



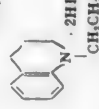

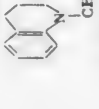
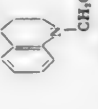
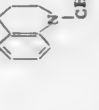
Ethylene sulfide differs from ethylene oxide in that it reacts with tetrahydroquinoline in benzene solution to form N-(β -mercaptoethyl)tetrahydroquinoline in a low yield ($\approx 7\%$). When the reaction was tried in an alcoholic solution and also in the absence of a solvent, ethylene sulfide polymer was formed quantitatively. N-(β -mercaptoethyl)-tetrahydroquinoline was identified in the form of the base and in the form of a salt, and also by the fact that air oxidation converted it into the corresponding disulfide.

Attempts to react tetrahydroquinoline with ethylenimine were unsuccessful even though quite a wide range of experimental conditions was tried (heating the reactants in sealed tubes at 120° without a solvent, use of different solvents, use of catalysts, etc.). In all experiments with ethylenimine only ethylenimine polymer and unreacted tetrahydroquinoline were isolated.

N-Aminoalkyl derivatives of tetrahydroquinoline were prepared either by reducing the corresponding nitriles or by condensing tetrahydroquinoline with β - and γ -halo alkylamines.

The synthesis of N-(β -cyanoethyl)-tetrahydroquinoline was carried out as described in the literature [7]; the reduction of the

N-Substituted 1, 2, 3, 4-Tetrahydroquinolines

No.	Formula	Empirical formula	B. p. (pressure in mm)	Melting point	n_D^{20}	d_4^{20}	MH_2		% N		% S		Percent halogen		Molecular weight (potentiometric)		Yield, %
							calc.	found	calc.	found	calc.	found	calc.	found	calc.	found	
1		$C_{11}H_{15}ON$	140—144°	—	1.5740	1.1041	52.66	52.9	7.9	7.85	—	—	—	—	177	—	18.1
2		$C_{11}H_{16}ONBr$	—	120—122° (from alcohol)	—	—	—	—	—	—	—	—	31.0	30.78	258	276	—
3		$C_{13}H_{19}O_2N$	167—170°	—	1.5523	1.1055	63.44	63.8	6.33	6.15	—	—	—	—	221	—	15.4
4		$C_{13}H_{20}O_3N$	205—207	—	1.5420	1.1053	74.42	75.46	5.28	5.12	—	—	—	—	265	—	1.3
5		$C_{12}H_{18}N_2$	137—140	—	1.5777	1.0450	59.18	60.6	14.73	14.27	—	—	—	—	190	—	63
6		$C_{12}H_{20}N_3Br_2$	—	195—197 (from alcohol)	—	—	—	—	—	—	—	—	45.45	45.1	352	—	—
7		$C_{12}H_{15}O_2N$	—	70—72	—	—	—	—	6.8	6.8	—	—	—	—	205	198	73
8		$C_{11}H_{16}N_2$	130—132	—	1.5830	1.0645	55.76	55.26	15.9	16.0	—	—	—	—	176	—	7
9		$C_{11}H_{14}N_2$	160—161	—	1.5475	0.9836	77.75	77.85	12.07	12.4	—	—	—	—	232	—	10
10		$C_{11}H_{13}NS$	145	—	1.5990	1.0903	58.83	60.4	7.25	7.73	16.6	16.93	—	—	193	—	6.7

No. of derivative	Formula	Empirical formula	Boiling point (5 mm pressure)	Melting point	n_D^{20}	d_4^{20}	$M.R.$		% N		% S		Percent halogen		Molecular weight (potentiometric)		Yield %
							calc.	found	calc.	found	calc.	found	calc.	found	calc.	found	
11		$C_{11}H_{16}NSBr$	—	176–177° (from alcohol)	—	—	—	—	—	—	—	—	29.3	28.98	274	272	—
12		$C_{22}H_{30}N_2S_2Cl_2$	—	118–120 (from alcohol)	—	—	—	—	6.15	6.63	13.9	13.6	15.46	15.73	457	—	58
13		$C_{10}H_{10}NS_2K$	—	264–266 (from alcohol)	—	—	—	—	5.66	5.48	25.91	25.46	—	—	247	—	65
14		$C_{26}H_{24}O_2N_2$	—	173–174	—	—	—	—	7.07	7.5	—	—	—	—	396	—	57
15		$C_{18}H_{17}O_3N$	210°	63–65	—	—	—	—	4.7	4.78	—	—	—	—	295	—	30
16		$C_{20}H_{19}ON$	152	—	1.519	0.9872	92.7	91.98	4.68	4.8	—	—	—	—	299	—	23

The antioxidant properties of N-substituted tetrahydroquinolines were evaluated by their ability to inhibit the oxidative development of rancidity in bone fat, initiated by ultraviolet radiation. It is known [11] that peroxides are formed (as a result of a radical process) in the initiated oxidation of oils. One of the standard fat antioxidants is "ionol" (2,6-ditert.-butylhydroxytoluene). The antioxidant ability of 1,2,3,4-tetrahydroquinoline derivatives was compared with the effectiveness of "ionol", and it was shown that several compounds are equivalent to "ionol" in inhibiting the oxidative development of rancidity in fats.

Substances which showed an antioxidant effect equal to or somewhat greater than that of "ionol" were tested as corrosion inhibitors.

It should be noted that tetrahydroquinoline itself as well as its N-substituted derivatives did not inhibit the oxidative degradation of a styrene-acrylonitrile copolymer.

Some of these new N-substituted tetrahydroquinolines were found to possess repellent properties and were superior to standard repellents owing to their lower volatility and absence of an irritating effect on the skin.

EXPERIMENTAL

Hydroxyethylation of 1,2,3,4-Tetrahydroquinoline. A mixture of 266 g (2 moles) of 1,2,3,4-tetrahydroquinoline and one ml of water was placed in a three-necked flask equipped with a stirrer, thermometer, and bubbler. Gaseous ethylene oxide was passed in with continuous stirring (until absorption stopped); the temperature was kept at 25-30°. After repeated distillations the following were isolated: unreacted tetrahydroquinoline b.p. 94-95° (5 mm), 116 g; a monohydroxyethylated product (1) 48 g; a dihydroxyethylated product (3) 68 g; a trihydroxyethylated product (4) 7 g; nonvolatile residue 100 g.

N-(γ -Aminopropyl)-1,2,3,4-tetrahydroquinoline (5). A solution of 18.6 g (0.1 mole) of N-(β -cyanoethyl)-1,2,3,4-tetrahydroquinoline in 60 ml of alcohol was added slowly to a vigorously stirred suspension of 40 g of finely divided nickel-aluminum alloy in 80 ml of 1% sodium hydroxide; the temperature increased to 50-60°. The mixture was boiled for four hours, cooled and filtered. The filtrate was acidified (to Congo Red) with alcohol saturated with hydrogen chloride and evaporated to dryness under vacuum. The residual viscous mass was dissolved in a minimum quantity of water and the solution neutralized with 40% sodium hydroxide with cooling. The precipitated base was extracted with benzene and dried over potassium hydroxide, after boiling off the solvent it was distilled under vacuum. The base was insoluble in water, very soluble in alcohol, benzene, and acetone, and it formed a hydrobromide which was very soluble in water (6).

N-Tetrahydroquinolylpropionic Acid (7). Ten g (0.054 mole) of N-(β -cyanoethyl)-tetrahydroquinoline was boiled with alcoholic potassium hydroxide (5 g of potassium hydroxide, 10 ml of water, and 50 ml of alcohol) until the evolution of ammonia ceased. Most of the solvent was distilled off under vacuum and the residue was acidified with the calculated quantity of concentrated hydrochloric acid; the oil which separated was crystallized by allowing it to stand for a long time over sulfuric acid in a vacuum desiccator. The product was dissolved in benzene, treated with activated carbon and carefully evaporated under vacuum. The residue consisted of light-yellow needle-like crystals. It was insoluble in water, soluble in dilute alkalis and acids, very soluble in benzene, alcohol, and ether.

N-(β -Aminoethyl)-1,2,3,4-tetrahydroquinoline (8). Fifty ml of an alcoholic solution of sodium ethylate (0.2 mole) was added gradually to a solution of 13.3 g (0.1 mole) of tetrahydroquinoline and 22.9 g (0.1 mole) of β -bromoethylamine hydrobromide in 50 ml of alcohol at 60° while stirring continuously. The mixture was boiled for two hours, cooled, the sodium bromide filtered off, the alcohol boiled off and the residue distilled under vacuum. It was very soluble in alcohol, acetone, and ether, and insoluble in water.

N-(β -Diethylaminoethyl)-1,2,3,4-tetrahydroquinoline (9). A 100 ml volume of a solution of N-diethyl- β -chloroethylamine (0.3 mole) in anhydrous alcohol was added to a solution of 39.9 g (0.3 mole) of tetrahydroquinoline in 150 ml of alcohol at 60° while stirring continuously. The mixture was boiled on a water bath for five hours and evaporated to dryness under vacuum. The residual cherry-red crystalline mass was dissolved in a minimum quantity of water and was neutralized with 40% sodium hydroxide with cooling. The oil which separated was extracted with ether and dried over calcined magnesium sulfate. The ether was driven off and the residue distilled under vacuum.

N-(β -Mercaptoethyl)-1,2,3,4-tetrahydroquinoline (10). To a stirred solution of 26.6 g (0.2 mole) of tetrahydroquinoline in 80 ml of benzene at 50° was added 12 g (0.2 mole) of ethylene sulfide. The solution was boiled for five hours and the benzene distilled off under vacuum. The product was insoluble in water, very soluble in ether, alcohol, acetone, benzene; it formed a water-soluble hydrobromide (11).

β, β' -Bis-(N-1,2,3,4-tetrahydroquinolyl)-diethyldisulfide (12). A solution of 5.8 g (0.03 mole) of N-(β -mercaptoethyl)-tetrahydroquinoline in 150 ml of alcohol was oxidized at 50-60° with air in the presence of traces of ferrous sulfate. When the oxidation was complete (negative test for the SH group) the solution was filtered, the alcohol was distilled off under vacuum, the residue was treated with ether, the ether solution was dried with calcined sodium sulfate, and the solvent was distilled off. The residue - a nonvolatile yellow oil - was dissolved in 20% hydrochloric acid; the solution was decolorized with activated charcoal and evaporated under vacuum.

Potassium 1,2,3,4-Tetrahydroquinolyldithiocarbamate (13). Six ml of carbon disulfide was added to a suspension of 13.3 g (0.1 mole) of tetrahydroquinoline, 0.56 g (0.1 mole) of powdered potassium hydroxide in 30 ml of benzene and 5 ml of water while stirring continuously. A yellow crystalline precipitate separated which was filtered off after two hours, washed with cold alcohol and dried.

Phthaloyl-N,N'-bis-(1,2,3,4-tetrahydroquinoline) (14). To a solution of 33.2 g (0.25 mole) of tetrahydroquinoline in 100 ml of benzene at 0-5° was added gradually 12.5 g (0.062 mole) of phthaloyl chloride while stirring continuously. The mixture was boiled for three hours, then cooled and the precipitate filtered off. A further quantity of crude product separated when the benzene filtrate was evaporated under vacuum. The product was triturated with water in a mortar to remove the tetrahydroquinoline hydrochloride, transferred to a filter, washed several times with water and dried.

In a similar manner Product 15 was prepared from the acyl chloride of monomethyl phthalate.

N-Undecylenyl-1,2,3,4-tetrahydroquinoline (16). A mixture of 13.3 g (0.1 mole) of tetrahydroquinoline and 18.4 g (0.1 mole) of undecylenic acid was heated in an oil bath at first for five hours at 170°, then for three hours at 230°, after which the reaction mixture was distilled under vacuum. The product was insoluble in alkalis, quite soluble in organic solvents, and was decolorized by bromine-water.

SUMMARY

Several new N-substituted 1,2,3,4-tetrahydroquinolines were synthesized and characterized. Some of these compounds were found to be very effective repellents and showed promise as antioxidants.

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SOME DERIVATIVES OF PYRAZOLIDONE-3

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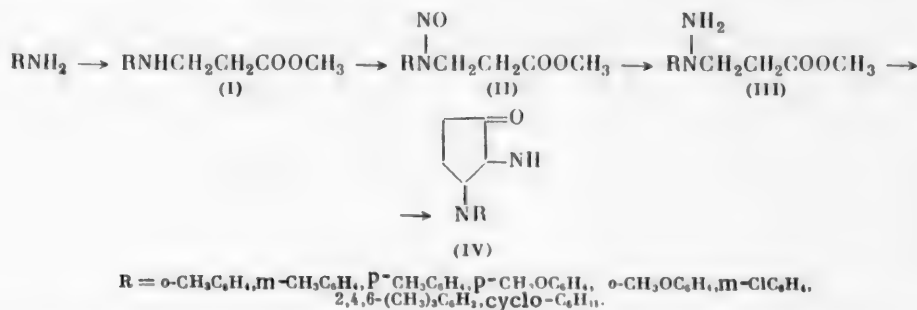
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A considerable number of papers devoted to the synthesis of derivatives of 1-phenylpyrazolidone-3 ("phenidone") have appeared in the literature in recent years. Compounds of this type are of interest to research workers because "phenidone" and its derivatives when used in place of metol in a developing solution containing hydroquinone give rise to the phenomenon of so-called superadditivity, which increases markedly the activity of hydroquinone as a developer. The mechanism of this interesting phenomenon is described in [1].

The purpose of the present work was to synthesize several derivatives of pyrazolidone-3 and to examine their photographic properties.

The following methods of synthesizing compounds of this type are among those published in the literature: 1) reaction of an arylhydrazine with β -halo propionic acids or their esters [2] or acyl chlorides [3]; 2) cyclization of esters of β -(α -arylhydrazine)propionic acid [4] or of hydrazides of β -hydroxypropionic acid [5]; 3) acidic hydrolysis of 3-aminopyrazolines [6]; 4) reaction of an arylhydrazine with acrylic acids [7], their esters [8], or amides [9].

In preparing derivatives of pyrazolidone-3 we used a scheme proposed for the synthesis of "phenidone" which started with the corresponding amine: addition of methyl acrylate to the amine, nitrosation of the resulting secondary amine (I), reduction of the nitrosamine (II) to the corresponding hydrazine (III), and cyclization of the latter to 1-aryl (cycloalkyl)pyrazolidone-3 (IV), without separating products (II) and (III).



This scheme was found satisfactory also for the preparation of 1-cyclohexyl-4-methylpyrazolidone-3 starting with cyclohexylamine and methyl methacrylate although it should be noted that we did not succeed in adding methyl methacrylate to aniline under our experimental conditions. The first four of the compounds shown above have been described previously. The constants of the compounds synthesized agreed with literature data with the exception of (IV) ($R = m\text{-CH}_3\text{C}_6\text{H}_4$): the melting point which we found was much lower than the literature value, but the elementary analysis and the photographic properties of this compound left no doubt about its structure.

The photographic properties were tested by the usual sensitometric method. Metol was substituted with derivatives of "phenidone" in "Chibisov's developer". The control was metol-hydroquinone, and all results of photographic tests on "phenidone" derivatives were compared with those obtained on the control developer. The photographic test data showed that the pyrazolidone-3 derivatives, with the exception of two cyclohexyl derivatives, activated hydroquinone in developing solutions sufficiently well that they may be used as substitutes for metol in metol-hydroquinone developers.

EXPERIMENTAL

Methyl β -(m-Methylphenylamino)propionate. A mixture of 53.7 parts of m-toluidine, 25 moles of glacial acetic acid, and 44.7 g of methyl acrylate was heated for three hours on a water bath. The reaction mixture was cooled and poured into 100 ml of water, the oil which separated was extracted with ether, the ether extract was washed with water, dried with sodium sulfate, the ether driven off, and the residue distilled under vacuum. Yield 70.5 g (73%); b.p. 167-168° (8 mm) n_D^{20} 1.5382.

Found %: C 68.43, 68.33; H 8.00, 7.80; N 7.31, 7.24. $C_{11}H_{15}O_2N$. Calculated %: C 68.70; H 7.90; N 7.29.

Similarly the following compounds were prepared from methyl acrylate and the corresponding aniline derivatives.

Methyl β -(o-Methoxyphenylamino)propionate in a yield of 50%. B.p. 182-183° (15 mm) n_D^{20} 1.5408.

Found %: C 63.33, 63.15; H 7.58, 7.43; N 6.75, 6.69. $C_{11}H_{15}O_3N$. Calculated %: C 63.14; H 7.22; N 6.69.

Methyl β -(m-Chlorophenylamino)propionate in a yield of 49% (reaction time six hours). Colorless plates with m.p. 43-44° (from aqueous methanol). Literature value of m.p. 39.6-40.6° [10].

Found %: N 6.32, 6.31; Cl 16.84, 16.73. $C_{10}H_{12}O_2NCl$. Calculated %: N 6.55; Cl 16.61.

Methyl β -(p-Methylphenylamino)propionate in a yield of 90%. Colorless plates with m.p. 54-56° (from petroleum ether). Literature value of m.p. 60-61° [11].

Found %: C 68.71, 68.92; H 7.77, 7.98; N 7.33, 7.52. $C_{11}H_{15}O_2N$. Calculated %: C 68.70; H 7.90; N 7.29.

Methyl β -(o-Methylphenylamino)propionate in a yield of 62%. B.p. 140-141° (4 mm), 156° (8 mm), n_D^{20} 1.5385. Literature value of b.p. 142-148° (5.5 mm) [12].

Found %: N 7.00, 7.16. $C_{11}H_{15}O_2N$. Calculated %: N 7.29.

Methyl β -(2,4,6-Trimethylphenylamino)propionate in a yield of 33%. B.p. 156° (6 mm), n_D^{20} 1.5260.

Found %: N 6.40, 6.46. $C_{13}H_{19}O_2N$. Calculated %: N 6.47.

Methyl β -(p-Methoxyphenylamino)propionate in a yield of 55%. M.p. 37-38° (mixture of benzene and petroleum ether). Literature value of m.p. 37.6-38.2° [11].

1-(m-Tolyl)pyrazolidone-3. A cold solution of 37.2 g of sodium nitrite in 48 ml of water was added to a vigorously stirred solution of 70.5 g of methyl β -(m-methylphenylamino)propionate in 39 ml of glacial acetic acid at 0°. The reaction mixture was kept at room temperature for one hour. The product was extracted with ether, the ether extract dried with sodium sulfate, and the ether boiled off. The residual oily product (74 g) was dissolved in 105 ml of glacial acetic acid, and 60 g of zinc powder was added slowly with stirring to the solution at 0°. The temperature of the reaction mixture did not rise above 5°. The mixture was allowed to stand over night at room temperature, 600 ml of water was added and the mixture boiled for three hours, after which the excess of zinc was removed by filtering the hot reaction mixture. When cooled a precipitate separated which was filtered off, washed with water and dried with calcium chloride. Yield 30 g (46%), calculated on the original methyl ester. Colorless plates with m.p. 114-116° (from benzene). Literature values of m.p. 178-179° [5], 163° [9].

Found %: C 68.43, 68.27; H 6.96, 6.41; N 15.83, 15.69. $C_{10}H_{12}ON_2$. Calculated %: C 68.15; H 6.86; N 15.89.

Similarly the following derivatives of pyrazolidone-3 were prepared.

1-(o-Methoxyphenyl)pyrazolidone-3. After the excess of zinc was filtered off and the reaction mixture cooled an oil separated which was extracted with chloroform, the extract washed with water, dried with calcium chloride, and the chloroform boiled off; some benzene was added to the residue, resulting in the formation of a precipitate which was filtered off and washed with ether. Yield 35%, calculated on the original methyl ester. Colorless rhombic crystals with m.p. 131-133° (from benzene).

Found %: C 62.50, 62.50; H 6.30, 6.23; N 14.52, 14.62. $C_{10}H_{12}O_2N_2$. Calculated %: C 62.48; H 6.29; N 14.57.

1-(m-Chlorophenyl)pyrazolidone-3. Yield 36%; After reprecipitation from a mixture of carbon tetrachloride and petroleum ether colorless rhombic crystals with m.p. 125-127°.

Found %: C 54.96; H 5.25; N 14.24, 14.18; Cl 17.82, 17.80. $C_9H_5ON_2Cl$. Calculated %: C 54.95; H 4.61; N 14.24; Cl 18.05.

1-(p-Tolyl)pyrazolidone-3. Yield 51%. Light-rose needles with m.p. 150-152° (from water). Literature value of m.p. 152° [5].

Found %: C 68.21, 68.41; H 6.83, 6.77; N 15.77, 15.94. $C_{10}H_{12}ON_2$. Calculated %: C 68.15; H 6.86; N 15.89.

1-(o-Tolyl)pyrazolidone-3. Yield 36%. Colorless plates with m.p. 196-197° (from aqueous alcohol). Literature value of m.p. 195-197° [5].

Found %: N 16.05, 15.98. $C_{10}H_{12}ON_2$. Calculated %: N 15.89.

1-(2,4,6-Trimethylphenyl)pyrazolidone-3. Yield 22%. Colorless leaflets with m.p. 127.5-129° (from a mixture of carbon tetrachloride and petroleum ether).

Found %: C 70.05, 70.28; H 7.85, 7.68; N 13.87, 13.69. $C_{12}H_{16}ON_2$. Calculated %: C 70.55; H 7.89; N 13.71.

1-(p-Methoxyphenyl)pyrazolidone-3. Yield 33%. After extraction with chloroform and evaporation light-rose needles were obtained melting at 144-146° (from a mixture of carbon tetrachloride and petroleum ether). Literature value of m.p. 146° [5].

Found %: C 62.66, 62.55; H 6.08, 6.20; N 14.58, 14.58. $C_{10}H_{12}O_2N_2$. Calculated %: C 62.48; H 6.29; N 14.57.

1-Cyclohexylpyrazolidone-3. A mixture of 60 g of cyclohexylamine, 200 ml of anhydrous alcohol [13], and 56.7 g of methyl acrylate was boiled for 20 hours on a water bath, the alcohol distilled off and the product obtained by extracting the aqueous solution with chloroform and evaporating the extract. Yield 35%, calculated on the original cyclohexylamine. Colorless needles with m.p. 88-90° (from petroleum ether).

Found %: C 64.28, 64.48; H 9.61, 9.67; N 16.37, 16.52. $C_9H_{16}ON_2$. Calculated %: C 64.24; H 9.58; N 16.65.

1-Cyclohexyl-4-methylpyrazolidone-3 was prepared similarly from cyclohexylamine and methyl methacrylate in a yield 36%. Colorless plates with m.p. 124-126° (from petroleum ether).

Found %: C 65.68, 65.74; H 10.22, 10.04; N 15.57, 15.65. $C_{10}H_{18}ON_2$. Calculated %: C 65.89; H 9.95; N 15.37.

SUMMARY

Several derivatives of pyrazolidone-3 were synthesized and their photographic properties studied.

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REDUCTION OF NAPHTHOL CARBOXYLIC ACIDS

V. INDIRECT ELECTROREDUCTION OF 2-NAPHTHOL-1-CARBOXYLIC ACID

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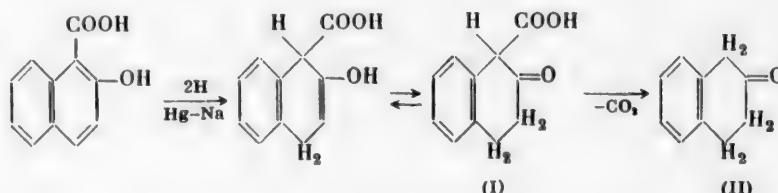
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The difference in the behavior of 1-naphthol-2-carboxylic acid and 2-naphthol-3-carboxylic acid on indirect electroreduction [1] has induced us to study the reduction of the third available isomer - 2-naphthol-1-carboxylic acid - under the same conditions. The investigation has shown that this hydroxy acid, like the 2,3-isomer, reduces only in the nucleus.

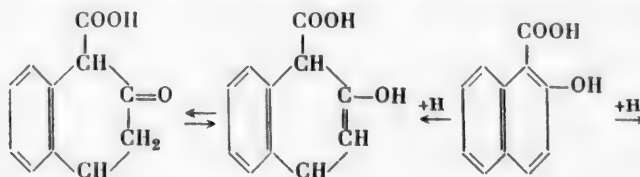


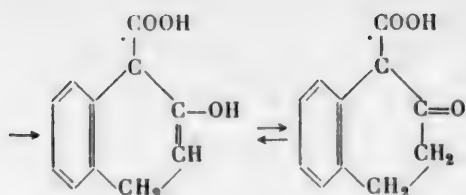
The main reaction product is 2-tetralone-1-carboxylic acid (I), the isolation of which from the reduction solution presents considerable difficulties in consequence of its instability. In the pure form this β -ketoacid has m.p. 123-125° (with decomp.) and may be stored at a temperature not higher than +5° for an extended period (up to six months), but in weakly acid and weakly alkaline solutions it decarboxylates even during the reduction process. The optimum conditions for carrying out the reduction so that its decarboxylation does not take place to an appreciable extent during the process are: reaction temperature not above 5°, pH of the solution reduced 6-7. However, in spite of all precautions, it was impossible to isolate the β -ketoacid in good yields; therefore we estimated the amount of it formed during reduction from the yield of β -tetralone (II), which, under the conditions of the complete decarboxylation of 2-tetralone-1-carboxylic acid is 30-40%.

In addition to β -tetralone, three other colorless crystalline compounds were isolated from the products of this reaction: (1) m.p. 272° (sublimes) (A, yield 6-34%), dioxime, m.p. 290-293°; (2) m.p. 198-200° (B, yield 5-13%), monooxime, m.p. 200-202°; (3) m.p. 167-170° (C, yield 1-2%), dioxime, m.p. 246-247°. They all have a molecular weight double that of β -tetralone, and their elementary composition corresponds to the single molecular formula $C_{20}H_{18}O_2$. These isomeric substances consist of the products of the combination of two β -tetralone residues. One of them (B) forms only a monooxime. Probably this is explained by a peculiarity of its structure which allows the reaction of only one of its two carbonyl groups with hydroxylamine.

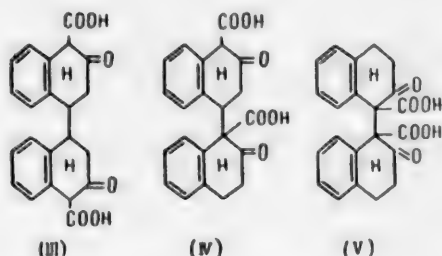
The formation of these diketones is the result of reductive dimerization, noted by a number of chemists in the reduction under similar conditions of such compounds as, for example, the derivatives of acrylic [2], phthalic [3], opianic [4], benzaldehyde- α -carboxylic [5], hemipinic [6], and some other acids.

In our case, reductive dimerization may take place through the intermediate formation of two different radicals

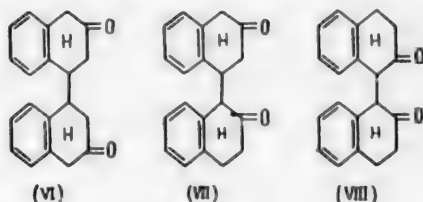




the recombination of which must lead to the formation of the following three isomeric diketoacids (without taking possible stereoisomers into account):



In working up the reaction mass, the latter decarboxylate, forming the corresponding diketones.



Up to the present, we have not succeeded in establishing which of these three structural formulas (VI, VII, VIII) correspond to each of the diketones isolated (A, B, C).

In order to detect products of the reduction of 2-naphthol-1-carboxylic acid at the carboxyl group, its reduction was carried out in the presence of *p*-toluidine. However, the addition of *p*-toluidine to the reaction mixture only promoted the decomposition of the 2-tetralone-1-carboxylic acid. No products of the reduction of 2-naphthol-1-carboxylic acid at the carboxyl group could be isolated from the reaction mixture. Only *o*-carboxyphenylpropionic acid was found in small amount (about 6%); this is formed, apparently, as the result of an oxidative-hydrolytic decomposition of β -tetralone.

EXPERIMENTAL

2-Naphthol-1-carboxylic acid was obtained by a method suggested by V.M. Rodionov [7]. The acid, recrystallized from aqueous alcohol, had m.p. 156-157°, which corresponds with the data given in the literature [7, 8]. This preparation contains water, according to the analysis given in reference [7], which corresponds to the formula $4C_{11}H_8O_3 \cdot H_2O$. The acid used for the investigation was twice recrystallized from benzene; it had m.p. 181-182° and did not contain water.

Found %: C 70.20, 70.16; H 4.49, 4.80. $C_{11}H_8O_3$. Calculated %: C 70.20; H 4.26.

Reduction of 2-naphthol-1-carboxylic acid. Twenty grams of 2-naphthol-1-carboxylic acid was dissolved in sodium carbonate solution (10 g of Na_2CO_3 in 300 ml of water). The solution was filtered, 40 g of boric acid was added and the mixture was poured into the electrolyzer [1]. A current of 5A was passed for 2 hours. The temperature was maintained not above 5°, the electrolyzer being placed in an ice bath, and 100 g of ice being added gradually to the reduction solution. The pH of the solution was maintained between 6 and 7 by the addition of 5% hydrochloric acid (total consumption, 150 ml). After the current had been switched off, the solution was stirred for another half-hour at the same temperature. The reduced solution was acidified with 30% sulfuric acid and subjected to steam distillation. β -Tetralone (the 2-tetralone-1-carboxylic acid decarboxylated completely) and its conversion product - *o*-carboxyphenylpropionic acid - collected in the distillate. A mixture of the diketones (A, B, and C) remained in the distillation flask.

1. The β -tetralone was extracted from the steam distillate with ether. The extract was dried with sodium sulfate; the residue after removal of the ether was distilled in vacuum. A yield of 6.4 g (42%) of a fraction with b.p. 106-110° (4 mm), n_D^{20} 1.5600 was obtained. Literature data [9]: b.p. 111-115° (5 mm), n_D^{20} 1.5594.

2,4-Dinitrophenylhydrazone - m.p. 145-147°. A sample mixed with a known preparation gave no depression of the melting point.

2. o-Carboxyphenylpropionic acid was isolated from the residue after the vacuum distillation of the β -tetralone by triturating with benzene. The yield was 1.25 g (6%), m.p. 167-168° (from benzene and alcohol). Literature data [10]: m.p. 167°. A sample in admixture with a preparation obtained by the oxidation of tetralin exhibited no depression of the melting point.

Found %: C 61.98, 62.12; H 5.31, 5.27. Acid number 578. $C_{10}H_{10}O_4$. Calculated %: C 61.85; H 5.19. Acid number 576.

3. The di- β -tetralone with m.p. 272° (A). The reduction products non-volatile in steam, which solidified on cooling, were separated from the water (8.65 g), ground, and heated with 25 ml of methanol. A considerable part of the material went into solution, and the insoluble white residue (1.9 g or 13%) had m.p. 272° (from dioxane, sublimes).

The yield in different experiments varied from 6 to 34%.

The substance is insoluble in alcohol, ether, and benzene, and sparingly soluble in acetone and acetic acid.

Found %: C 82.34, 82.54; H 6.20, 6.37. M 320 (Rast). $C_{20}H_{18}O_2$. Calculated %: C 82.79; H 6.25. M 290.

Dioxime - fine crystals, m.p. 290-293°; insoluble in the usual solvents.

Found %: N 8.75, 8.85. $C_{20}H_{20}O_2N_2$. Calculated %: N 8.75.

Di-2,4-dinitrophenylhydrazone - red needles with m.p. 235-237° (from alcohol).

Found %: N 17.76, 17.77. $C_{32}H_{26}O_8N_8$. Calculated %: N 17.22.

4. The di- β -tetralone with m.p. 198-200° (B). The solvent was removed from the methanol solution (see above), the residue was dissolved in 40 ml of ether and left overnight in a closed vessel. The crystals which separated (~1 g) were filtered off: m.p. 198-200° (from benzene).

Found %: C 82.72, 82.67; H 6.43, 6.88. M 270 (Rast). $C_{20}H_{18}O_2$. Calculated %: C 82.79; H 6.25. M 290.

Monooxime - colorless crystals with m.p. 200-202° (from aqueous alcohol).

Found %: N 4.77, 4.73. $C_{20}H_{19}N_2$. Calculated %: N 4.59.

In some experiments, the diketone (B) could be isolated only by the following procedure. The ethereal solution was washed (from phenolic products) three times with 5% NaOH, and then with water, 10% acetic acid, bicarbonate, and water again. The solution was dried with sodium sulfate. The ether was partially distilled off until crystallization of the diketone began; an additional 0.63 g was obtained.*

The yield varied from 5 to 13%.

5. The di- β -tetralone with m.p. 168-170° (C). The ethereal filtrate after the separation of the diketone (B) was diluted with ether and dried with sodium sulfate, and the solvent was removed. The residue (3.0 g) was distilled in vacuum and the fraction with m.p. 200-230° (0.5 mm) was collected. On triturating this fraction with ether, crystals (0.1 g) with m.p. 168-170° (from benzene) were isolated.

Found %: C 82.70, 82.62; H 6.34, 6.35. M 304 (Rast). $C_{20}H_{18}O_2$. Calculated %: C 82.79; H 6.25. M 290.

Dioxime - colorless needles, m.p. 246-247° (from aqueous alcohol).

Found %: N 8.54, 8.56. $C_{20}H_{20}O_2N_2$. Calculated %: N 8.75.

6. 2-Tetralone-1-carboxylic acid. The isolation of this ketoacid from the reaction mixture had to be carried out under mild conditions in order not to provoke its decomposition, which took place readily in the presence of foreign

* Sometimes the diketone (B) crystallized out from the ethereal solution with the diketone (C) (see below). In this case, the crystals (after recrystallization from benzene) were separated mechanically.

substances. The reduced solution (see 1) was cooled to 1-2° and acidified with 10% sulfuric acid cooled to 0°. The precipitate which separated was rapidly treated with ether. The ethereal extract was shaken three times with 10% sodium carbonate. On acidifying the sodium carbonate solution, with cooling, a pink precipitate was formed which was rapidly separated from the acid solution and transferred into cooled water. Then it was carefully filtered off with suction, washed with cold water, and dried at room temperature. The yield was 3-5 g (15-25%). After recrystallization from a large volume of CCl₄ at 40°, with subsequent distillation of part of the solvent in vacuo, it had m.p. 125-126° (with decomp.).

Found %: C 69.63, 69.73; H 5.28, 5.59. C₁₁H₁₀O₃. Calculated %: C 69.47; H 5.26.

SUMMARY

1. It has been shown that 2-naphthol-1-carboxylic acid on indirect electroreduction, like the 2,3-isomer, hydrogenates in the nucleus containing the substituents to the 1,4-dihydro derivative. The 2-tetralone-1-carboxylic acid formed can be isolated with a yield of 15-25%.

2. In contrast to 2-naphthol-3-carboxylic acid, this process, with the 2-naphthol-1-carboxylic acid, is accompanied by reductive dimerization, which leads to the formation of three isomeric di-β-tetralones with a total yield of about 30-40%.

3. The carboxyl group in 2-naphthol-1-carboxylic acid, in contrast to that of the 1,2- and 2,3-isomers, does not undergo reduction under these conditions.

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SYNTHESIS OF ACETALS BASED ON THE VINYL ETHERS OF *n*-BUTYL- AND CROTYLETHANOLS

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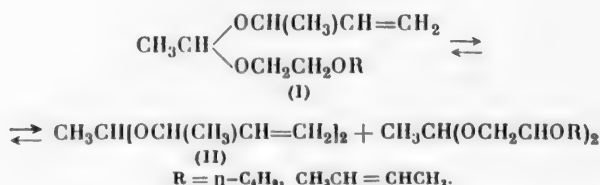
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Acetals based on crotyl and α -methylallyl alcohols have been obtained earlier [1]. The aim of the present work was the synthesis and study of the properties of acetals of α -methylallyl alcohol and vinyl ethers of monoethers of ethylene glycol.

It has been shown that the mixed acetals (I) transesterify on distillation in vacuum to form the symmetrical acetals (II) [2].



The acetals isolated (I, II) were characterized. They form mobile colorless liquids. The double bonds were determined by hydrogenation in alcohol with a nickel catalyst. The purity of the compounds obtained was estimated by oximation (from the amount of acetaldehyde isolated on hydrolysis).

EXPERIMENTAL

The vinyl ethers were synthesized from the alcohols and acetylene by the Favorskii-Shostakovskii method at 150°.

α -Methylallyl alcohol (b.p. 96-98°, n_D^{20} 1.4150) was obtained by saponifying the corresponding bromide.

Reaction of the vinyl ether of butoxyethanol with α -methylallyl alcohol. To a mixture of 19.1 g of the vinyl ether of butoxyethanol (b.p. 70-72° at 20-21 mm, d_4^{20} 0.8653, n_D^{20} 1.4213) and 150 g of α -methylallyl alcohol, a drop of hydrochloric acid was added with careful stirring. The temperature immediately rose to 48°. The mixture was left overnight, and was then treated with potash, filtered, and fractionated. The distillation yielded:

1st fraction - a mixture of di- α -methylallyl acetal and α -methylallyl *n*-butoxyethyl acetal.

2nd fraction - 19.7 g (62.7%) - α -methylallyl *n*-butoxyethyl acetal. b.p. 110° (13 mm), d_4^{20} 0.8851, n_D^{20} 1.4240, MR_D 62.30; calc. 62.08.

Found %: C 66.88, 66.66; H 10.03, 9.96. M 218. $C_{12}H_{24}O_3$. Calculated %: C 66.62; H 11.18. M 216.3.

Found %: acetaldehyde, 97.3, 97.8.

3rd fraction - 5.1 g (30%) - di-*n*-butoxyethyl acetal. b.p. 154° (25 mm), d_4^{20} 0.9115, n_D^{20} 1.4270, MR_D 73.50; calc. 73.42.

Found %: C 64.37, 64.34; H 11.19, 11.23. M 267.3. $C_{14}H_{30}O_4$. Calculated %: C 64.08; H 11.52. M 262.4.

Found %: acetaldehyde, 102.4, 110.2.

Reaction of the vinyl ether of crotyloxyethanol with α -methylallyl alcohol. The reaction between 22.1 g of the vinyl ester of crotyloxyethanol (b.p. 77-80° at 21-22 mm, d_4^{20} 0.8953, n_D^{20} 1.4410) and 17 g of α -methylallyl alcohol in the presence of a drop of hydrochloric acid yielded:

1st fraction - a mixture of dicrotyloxyethyl and α -methylallyl crotyloxyethyl acetals.

2nd fraction - 17.1 g (52.1%) - α -methylallyl crotyloxyethyl acetal. b.p. 116.8 (15 mm), d_4^{20} 0.9076, n_D^{20} 1.4380, MR_D 61.97; calc. 61.61.

Found %: C 67.09, 67.51; H 10.15, 10.09. M 207.1. $C_{12}H_{22}O_3$. Calculated %: C 67.25, H 10.34, M 214.3.

Found %: acetaldehyde, 100.4, 100.4.

3rd fraction - 3.1 g (15.2%) - dicrotyloxyethyl acetal. b.p. 150° (23-24 mm), d_4^{20} 0.9505, n_D^{20} 1.4490, MR_D 72.41, calc. 72.49.

Found %: C 65.45, 65.33; H 9.82, 9.85. M 257.2. $C_{14}H_{26}O_4$. Calculated %: C 65.08; H 10.14. M 258.3.

Found %: acetaldehyde, 109.0.

Hydrogenation was carried out at normal pressure in alcohol with a nickel catalyst. The catalyst was filtered off, the alcohol was removed by distillation, and the residue was distilled in vacuum.

1. Hydrogenation of 3.4 g of α -methylallyl n-butoxyethyl acetal was carried out. The absorption of hydrogen amounted to 400 ml (103%). A yield of 2.95 g (84.5%) of s-butyl n-butoxyethyl acetal was obtained. b.p. 116° (15 mm), d_4^{20} 0.8761, n_D^{20} 1.4197, MR_D 63.00; calc. 62.54.

2. The hydrogenation of 2.6 g of α -methylallyl crotyloxyethyl acetal was carried out. The absorption of hydrogen amounted to 582 ml (103%). A yield of 2.05 g (76%) of s-butyl n-butyloxyethyl acetal was obtained. b.p. 118.2° (15 mm), d_4^{20} 0.8768, n_D^{20} 1.4198, MR_D 62.98; calc. 62.54.

Found %: C 66.23, 66.22; H 10.64, 10.75. M 215.0. $C_{12}H_{26}O_3$. Calculated %: C 66.01; H 12.00. M 218.3.

Found %: acetaldehyde, 99.3, 99.9.

3. Hydrogenation of 1.3 g of dicrotyloxyethyl acetal was carried out. The absorption of hydrogen was 246 ml (104%). A yield 0.9 g (65.7%) of di-n-butyloxyethyl acetal was obtained. b.p. 150° (24-25 mm), d_4^{20} 0.9131, n_D^{20} 1.4264, MR_D 73.68; calc. 73.42.

SUMMARY

1. α -Methylallyl n-butoxyethyl, di-n-butoxyethyl, α -methylallyl crotyloxyethyl, dicrotyloxyethyl and s-butoxyethyl n-butoxyethyl acetals have been obtained and characterized.

2. It has been established that mixtures of α -methylallyl n-butoxyethyl and α -methylallyl crotyloxyethyl acetals partially transesterify with the formation of the symmetrical acetals.

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INVESTIGATIONS IN THE FIELD OF POLYMETHYLENE RINGS

XXXVII. CONVERSIONS OF POLYHALOGENO-SUBSTITUTED DERIVATIVES OF CYCLOPENTANE

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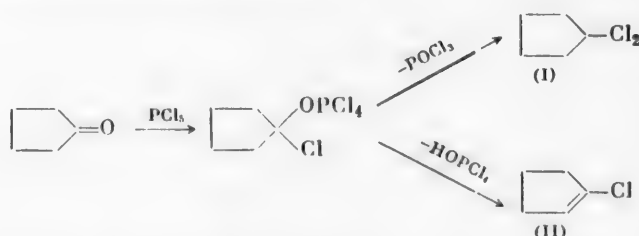
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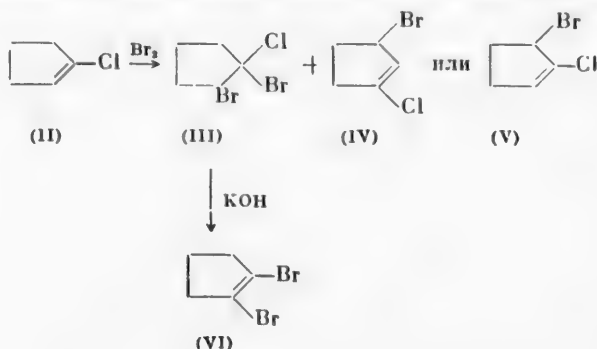
A.E. Favorskii and his students showed that stereospecificity is observed in the course of the reactions of eliminating hydrogen halides and halogens from mixed chlorobromo-substituted hydrocarbons of the aliphatic and cyclic series with various reagents [1]. The stereospecific character of the course of these reactions was considered by Favorskii in the light of the structure and stereochemistry of the molecules of the hydrocarbons with open and cyclic chains. However, at the present time, this view is insufficiently conclusive and has no experimental basis. The present investigation was undertaken with the aim of studying further and gaining an understanding of this question.

The reaction of cyclopentanone with phosphorus pentachloride led to a mixture consisting of 12% of 1,1-dichlorocyclopentane and 57% of 1-chlorocyclopent-1-ene (II)



Studying this reaction, Braude and Forbes [2] isolated yet a third product, with b.p. 111-113° which, in contrast to 1-chlorocyclopent-1-ene, was unstable and very readily gave a precipitate with silver nitrate, and which they assumed to be 1-chlorocyclopent-2-ene. Working with all precautions, we did not isolate this product. The dichloride (I) is stable on storage and only gives hydrogen chloride with difficulty on heating with 20% alcoholic caustic potash, being converted into the monochloride (II).

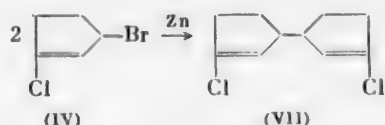
The addition of bromine to 1-chlorocyclopent-1-ene (II) leads to the formation of a mixture of products consisting of 40% of 1-chloro-1,2-dibromocyclopentane (III) and 20% of an unsaturated chlorobromide (IV) or (V), i.e., the reaction proceeds simultaneously in a normal and an abnormal fashion, which is a well-known phenomenon.



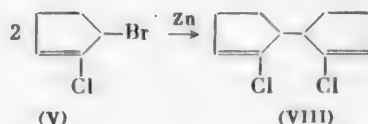
It was necessary to settle the question of which formula, (IV) or (V), corresponds to the structure of this unsaturated chlorobromide. It was impossible to do this using chemical methods of demonstrating the structure. Since the unsaturated chlorobromide (IV) or (V) gave a copious precipitate of silver bromide extremely readily with silver nitrate, the presence of an allyl bromine atom in it is not a matter of doubt. The chlorobromide readily adds bromine and gives a tribromochloride: either 3-chloro-1,2,3-tribromocyclopentane, corresponding to formula (IV), or 2-chloro-1,2,3-tribromocyclopentane, corresponding to formula (V). On oxidation and ozonization, the chlorobromide gives succinic acid, which makes the two structures (IV) and (V) equally probable. Hydrogenation led to cyclopentane, a monochloride, and dicyclopentene. It is again impossible to deduce the structure of the unsaturated chlorobromide from these hydrogenation products. It is also impossible to show the structure using spectroscopic methods, since the appearance of the same frequencies is to be expected for both forms.

The method of measuring dipole moments is more suitable than others for indicating the structure of the unsaturated chlorobromide (IV) or (V). The calculated dipole moment for formula (IV) is 2.63 D, and that for formula (V) is 3.49 D. The dipole moment found experimentally is 2.71 D. This value undoubtedly leads only to 1-chloro-3-bromocyclopent-1-ene (IV), and not to 1-chloro-2-bromocyclopent-1-ene (V).

In order to obtain further proof of the structure of the unsaturated chlorobromide, it was treated with zinc dust in anhydrous dioxane. It was expected that the zinc dust would link two molecules of the chlorobromide (IV) with the elimination of the two allyl bromide atoms, as a result of which a dimer of known structure (VII) would be obtained.



In fact, this reaction led to the dimer - 3,3'-dichlorobicyclopent-2-enyl (VII) with a yield of 35%. In addition, the reaction gave 1-chlorocyclopent-1-ene, formed by the reduction of the allyl bromine atom, and cyclopentene, formed by the reduction of both the allyl bromine atom and the chlorine atom attached to the double bond, which is well known and represents nothing new. If we were dealing with (V), the reaction with zinc dust would be expected to lead to the formation of a dimer with a structure (VIII)



In an attempt to hydrogenate the dimer obtained to dicyclopentane, the product of the addition of hydrogen to the double bond could not be isolated.

To determine the relative position of the double bonds in the dimer, the UV spectrum was obtained. In distinction from dicyclopent-1-enyl, which has an absorption maximum for conjugated double bonds at 240.3 mμ, this maximum was not found for the dimer we obtained. The action of sodium in dry ether on the dimer led to bicyclopent-2-enyl, which confirms the absence of a conjugated system of double bonds in it. No splitting took place in benzene solution on strong dilution. The measured dipole moment of the dimer was 2.29 D.

Theoretically, 3,3'-dichlorodicyclopent-2-enyl may exist in different forms according to the linkage of the two rings in the cis or trans positions. If internal rotation about the C-C linkage connecting the two rings takes place, four conformations are possible for the cis and trans linkage according to the angle of rotation of the rings with respect to one another ($\mu_\alpha = 0, 60, 120, \text{ or } 180^\circ$). If free rotation takes place, the mean dipole moment μ will be 2.82 D. But since, in fact, $\mu = 2.29 \text{ D}$, there is no free rotation about the C-C bond and, consequently, the most probable conformations of the dimer are the conformations spatially fixed in some definite way. The most energetically favorable conformation will be that in which the two rings are at an angle of 120° to one another ($\mu_{120^\circ} 2.22 \text{ D}$), with a small admixture of another conformation. The dipole moments cannot be used to distinguish 3,3'-dichlorobicyclopent-2-enyl (VII) from 2,2'-dichlorobicyclopent-2-enyl (VIII) since their values coincide for individual conformations.

The action of zinc dust in dry dioxane on 1,1-dichlorocyclopentane (I) and 1-chloro-1,2-dibromocyclopentane (III) yielded the products of the splitting out of hydrogen chloride - 1-chlorocyclopent-1-ene (II) and 1,2-dibromocy-

clopent-1-ene (VI), respectively. It is possible that zinc dust catalyzes this reaction, since at 60-70° both compounds are completely stable and hydrogen chloride is not split out even at a higher temperature.

It was shown that the action of metallic sodium in ether on the dimer (VIII) leads to the corresponding reduction product - bicyclopent-2-enyl (IX) - while the bicyclopentenyl with conjugated double bonds (X) is formed from 1-chloro-1,2-dibromocyclopentane (III).



On considering all the facts obtained together, it may be asserted that we are, in fact, dealing with 1-chloro-3-bromocyclopent-1-ene (IV) and 3,3'-dichlorobicyclopent-2-enyl (VII). This investigation forms a case when the investigator encounters insurmountable difficulties in solving the question of the proof of the structure of a molecule by purely chemical and some physical methods (for example optical methods). It is then necessary to use those methods of investigation by which unambiguous results may be obtained.

EXPERIMENTAL

Reaction of cyclopentanone with phosphorus pentachloride. To 400 g of phosphorus pentachloride ground to a powder, in 150 ml of petroleum ether, (20-30° fraction), 160 g of cyclopentanone in petroleum ether (1 : 1) was added dropwise with snow and salt cooling. After decomposing the mixture with water and ice, two fractions were isolated from the ethereal layer.

1st fraction - 100 g (53%) - 1-chlorocyclopent-1-ene (II). b.p. 105-107°, n_D^{20} 1.4663, d_4^{20} 1.0395, MR_α 27.33, C_5H_7Cl . Calculated 27.38. Literature data: b.p. 111-113°, n_D^{20} 1.4666 [2], d_4^{20} 1.044 [3]. The infrared spectrum exhibited an absorption band at 1642 cm^{-1} characteristic for a double bond.

2nd fraction - 30 g (20%) - 1,1-dichlorocyclopentane (I). b.p. 140-143°, n_D^{20} 1.4710, d_4^{20} 1.1828, MR_α 32.84, $C_5H_8Cl_2$. Calculated 32.68. Literature data: b.p. 143°, n_D^{20} 1.4701 [2].

Bromination of the monochloride. In a three-necked flask with a stirrer, condenser, and dropping funnel, was placed 135 g of the monochloride in dry chloroform (1 : 1). To the cooled solution, 62 ml of bromine in 90 ml of chloroform was added in drops. The greater part of the bromine was decolorized very rapidly, but towards the end decolorization was slow. The flask was cooled until the calculated amount of bromine had been added. The bromine which had not reacted was washed out with sodium sulfite solution, and the reaction mixture was washed several times with water and dried over calcium chloride.

The chloroform was sucked off in a vacuum, and the residue was repeatedly distilled. Two fractions were obtained.

1st fraction - 40 g (20%) - 1-chloro-3-bromocyclopent-1-ene (IV). b.p. 60-61° at 6 mm, n_D^{20} 1.5411, d_4^{20} 1.6076, MR_α 35.48, C_5H_6ClBr . Calculated 35.09. Literature data [4]: b.p. 60° at 3 mm, n_D^{20} 1.5385, d_4^{20} 1.586.

Found %: C 33.12, 32.96; H 3.61, 3.58; ClBr 63.88; Cl 20.59; Br 43.29. C_5H_6ClBr . Calculated %: C 33.06; H 3.31; ClBr 63.64; Cl 19.56; Br 44.08.

Dipole moment μ (benzene, 20°): found, 2.71 D. Calculated 2.63 D.

It slowly decolorizes a chloroform solution of bromine, and forms a precipitate with alcoholic silver nitrate and with sodium iodide in acetone. (Ag, Br, and NaBr were identified).

On oxidation with an aqueous acetic solution of permanganate in the presence of sodium carbonate, an acid with m.p. 182-184° was obtained, a mixed sample of which with authentic succinic acid (m.p. 185°) exhibited no melting point depression.

The absorption band in the infrared spectrum at 1632 cm^{-1} corresponded to a double bond.

2nd fraction (39%), 1-chloro-1,2-dibromocyclopentane (III). b.p. 87-89° at 5 mm, n_D^{20} 1.5597, d_4^{20} 1.9588, MR_α 43.32; calc. 43.29.

Found %: C 22.79, 22.78; H 2.32, 2.42; ClBr 74.16, 74.30. $C_5H_7ClBr_2$. Calculated %: C 22.86; H 2.17; ClBr 74.47.

The substance is stable to oxidation and does not liberate hydrogen halide on heating; with quinoline and pyridine it gives a resin. On heating to 40-50° with alcoholic caustic potash, it is converted into an insoluble amorphous resin and gives 1,2-dibromocyclopent-1-ene (VI):

b.p. 57° at 5 mm, n_D^{20} 1.5568, d_4^{20} 1.9282, MR_α 37.72; calc. 37.99.

Reaction of 1-chloro-3-bromocyclopent-1-ene (IV) with zinc dust. To a mixture of 71 g of zinc dust and 25 ml of anhydrous dioxane heated to 65°, 28 g of 1-chloro-3-bromocyclopent-1-ene was added dropwise in an atmosphere of nitrogen in the course of 1.5 hours. Heating and stirring were continued for a further 5 hours. After cooling, the solid matter was filtered off and washed with dioxane. The filtrate was diluted with a weak solution of hydrochloric acid, and the dioxane was removed by extraction with water. On distillation the following fractions were obtained:

1st fraction - 0.45 g (4.3%) - cyclopentene: b.p. 46-48°, n_D^{20} 1.4267, d_4^{20} 0.7752;

2nd fraction - 5.3 g (33%) - 1-chlorocyclopent-1-ene: b.p. 103-106°, n_D^{20} 1.4152, d_4^{20} 1.0378;

3rd fraction - 5.2 g (33%) - dichlorobicyclopentyl: b.p. 98-99° at 4 mm, n_D^{20} 1.5272, d_4^{20} 1.1970, MR_α 52.15; calc. 52.70.

Found %: C 58.90, 58.81; H 5.91, 6.01; Cl 34.86, 32.77. M 198. $C_{10}H_{12}Cl_2$. Calculated %: C 59.11; H 5.91; Cl 34.98. M 203.

An absorption frequency at 1640 cm^{-1} characteristic for double bonds was found in the infrared spectrum.

Dipole moment μ (benzene): found, 2.29 D; calculated, 2.82 D. For the various conformations the existence of which is determined by the angle α between the projections of the C-Cl bonds on a plane perpendicular to the C-C bond joining the two rings, the calculated dipole moments are: μ_0° 4.44 D; μ_{60° 3.85 D; μ_{120° 2.22 D; μ_{180° 0 D.

Bicyclopentyl. Hydrogenation of 25 g of the dimer in 15 ml of alcohol was carried out over a Pd/CaCO₃ catalyst. The yield was 1.7 g (60%).

B.p. 188-189°, n_D^{20} 1.4655, d_4^{20} 0.8695. Literature data [5, 6]: b.p. 188-190°, n_D^{20} 1.4654, d_4^{20} 0.8665.

The reaction of 1,1-dichlorocyclopentane (I) with zinc dust was carried out under the same conditions. The reaction mixture consisted of 30 g of the dichloride, 20 ml of anhydrous dioxane, and 56 g of zinc dust. After distilling the reaction products, 1-chlorocyclopent-1-ene was obtained. Yield, 14 g (64%).

b.p. 105-109°, n_D^{20} 1.4655, d_4^{20} 1.0359.

Reaction of 1-chloro-1,2-dibromocyclopentane (III) with zinc dust. Similarly, 50 g of the chlorodibromide, 150 g of zinc dust, and 50 ml of dry dioxane yielded 11.5 g (39%) of the monochloride, and 4.5 g (11%) of the dibromide.

b.p. 51-54° at 3 mm, n_D^{20} 1.5550, d_4^{20} 1.9061, MR_α 38.07; calc. 37.99.

Found %: Br 70.56, 70.65. $C_5H_6Br_2$. Calculated %: Br 70.88.

An absorption maximum in the infrared spectrum at 1634 cm^{-1} corresponds to a double bond.

On oxidation with an aqueous acetic solution of permanganate, glutaric acid with m.p. 90-91° was obtained; this gave no melting point depression with authentic glutaric acid.

Reaction of 1-chlorocyclopent-1-ene (II) with metallic sodium. In a flask with a reflux condenser and a calcium chloride tube was placed 7.5 g of metallic sodium in the form of freshly cut shavings in 30 ml of absolute ether. After the evolution of hydrogen had ceased, 11.3 g of 1-chlorocyclopent-1-ene was added. After two hours a reaction began with spontaneous heating. The ether began to boil and a reddish precipitate separated which was filtered off next day and washed with ether. On distillation, bicyclopent-1-enyl (X) (qualitative reaction for halogen negative) was obtained. Yield 2.4 g (33%).

B.p. 45-52° at 3 mm, n_D^{20} 1.5237, d_4^{20} 0.9254. Literature data [7]: b.p. 78-79° at 9 mm, n_D^{20} 1.5250, d_4^{20} 0.9260.

The reaction of 1-chloro-1,2-dibromocyclopentane (III) with metallic sodium was carried out in dry ether; 35 g of the initial compound yielded 4 g of bicyclopent-1-enyl and an amorphous resin which did not contain halogen.

The reaction of 3,3'-dichlorocyclopent-1-enyl with metallic sodium in ether led to a high-molecular-weight product and dicyclopent-2-enyl (IX) (0.7 g).

B.p. 40-55° at 2 mm, n_D^{20} 1.4910, d_4^{20} 0.9102. Literature data [6]: b.p. 54° at 8 mm, n_D^{20} 1.4939, d_4^{20} 0.9086.

It was characterized through the crystalline tetrabromide; m.p. 178-179° (from petroleum ether). Literature data [6]: m.p. 177-178°.

SUMMARY

1. It has been established that the reaction of bromine with 1-chlorocyclopent-1-ene takes place normally and abnormally at the same time with the formation of 1-chloro-1,2-dibromocyclopentane (40%) and 1-chloro-3-bromocyclopent-1-ene, respectively.

2. It has been shown that chemical and spectrometric methods are incapable of proving the structure of 1-chloro-3-bromocyclopent-1-ene, and only the method of measuring dipole moments is effective. The dipole moments of 1-chloro-3-bromocyclopent-1-ene and 3,3'-dichlorobicyclopent-2-enyl have been measured.

3. It has been established that the reaction of 1-chloro-3-bromocyclopent-1-ene with zinc dust gives three products: 1-chlorocyclopent-1-ene, cyclopentene, and 3,3'-dichlorobicyclopent-2-enyl, and the corresponding reaction with 1-chloro-1,2-dibromopentane gives two products: 1,2-dibromocyclopent-1-ene and 1-chlorocyclopent-1-ene.

4. By the action of metallic sodium, 1-chlorocyclopent-1-ene forms bicyclopent-1-enyl, 3,3'-dichlorobicyclopent-2-enyl forms bicyclopent-2-enyl, and 1-chloro-1,2-dibromocyclopentane forms bicyclopent-1-enyl.

5. It has been established that when 3,3'-dichlorobicyclopent-2-enyl is hydrogenated over a Pd/CaCO₃ catalyst, substitution of the chlorine atoms and the addition of hydrogen to the double bond proceed simultaneously.

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REARRANGEMENTS OF TRIAZENS

I. THE REARRANGEMENT OF UNSYMMETRICAL TRIAZENS INTO AMINOAZO COMPOUNDS

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The preparation of *o*-aminoazo compounds of the benzene series by direct azo coupling presents considerable difficulties [1]. Hence, the rearrangement of diazoamino compounds (triazens) has been used for the synthesis of *o*-aminoazo compounds [2]. The question of the ortho-rearrangement of triazens has not been elucidated to any extent in the literature, and a study of its mechanism is of interest. It was also important to investigate the production of unsymmetrical *o*-aminoazo compounds, the possibility of the formation of which has been denied [3].

In the present investigation, the rearrangement of unsymmetrical aromatic triazens with successively larger numbers of alkyl substituents on one of the aromatic components has been studied; 3,4-dimethylaniline was used as the second azo component. The reaction was carried out in a medium consisting of aromatic amines corresponding to the components of the initial triazen.

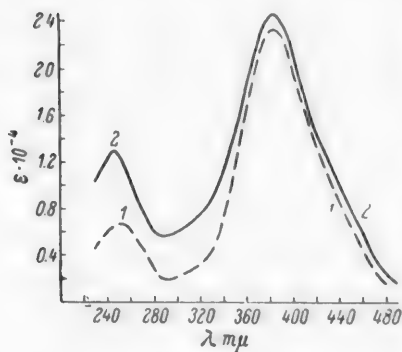
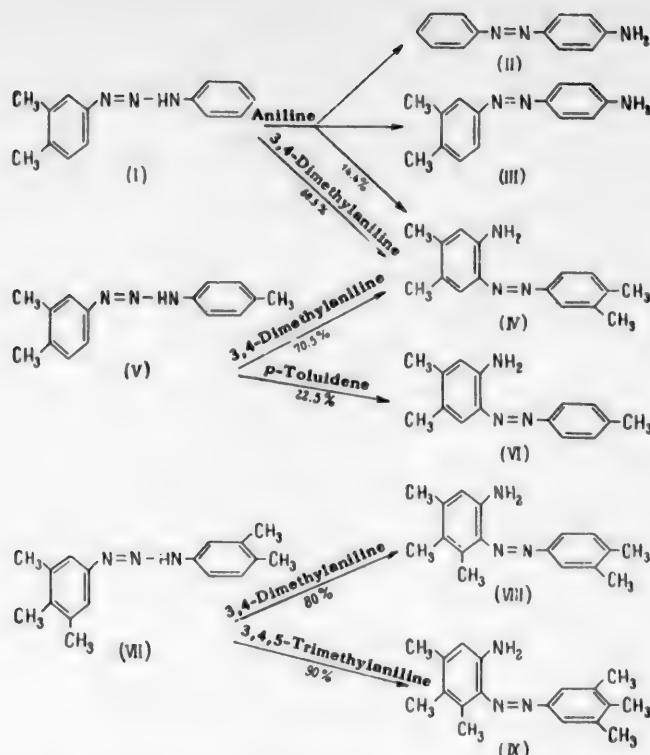


Figure 1. Absorption spectra (in alcohol). 1) 4-aminoazobenzene (II), 2) 3,4-dimethyl-4'-aminoazobenzene (III).

generation, which gave 3,4-dimethylaniline and *p*-phenylenediamine; its absorption spectrum (λ_{\max} 247 and 385 $m\mu$) indicated the conformity of the structure of compound (III) with the chromophoric system of 4-aminoazobenzene (Fig. 1). The structure of compound (IV) has been shown earlier [2]. The rearrangement of the unsymmetrical triazen (I) in 3,4-dimethylaniline gave sym. 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) as the main reaction product in good yield (60.5%).

The rearrangement of unsym. 1-(3',4'-dimethylphenyl)-3-(4"-tolyl)-triazene (V) in *p*-toluidine led to a mixture of dyes from which unsym. 3,4-dimethyl-6-(4'-tolylazo)-aminobenzene (VI) was isolated in a yield of 22.5%, together with a substance with m.p. 127-128°, having an absorption spectrum (λ_{\max} 327 and 440 $m\mu$) corresponding to that of an *o*-aminoazo compound, the structure of which has not yet been established. The production of the unsymmetrical *o*-aminoazo compound (VI) is the first case of the production of this type of dye in the rearrangement of triazens. Experiments in this direction undertaken previously [based on the rearrangement of unsym. 1-phenyl-3-(4'-tolyl)-

On rearranging unsym. 1-(3',4'-dimethylphenyl)-3-phenyltriazene (I) in aniline, the predominating reaction is the formation of the *p*-aminoazo compounds: 4-aminoazobenzene (II) and 3,4-dimethyl-4'-aminoazobenzene (III), together with 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV). Compounds (III) and (IV) cannot be obtained under the usual conditions of azo coupling, and special conditions are necessary for the synthesis of 4-aminoazobenzene (II) by direct azo coupling (IV). However, on rearranging diazoaminobenzene in aniline, 4-aminoazobenzene is formed with only 4% of the ortho isomer (V). The formation of the symmetrical *o*-aminoazo dye (IV), the structure of which does not correspond to the initial triazen, is a curious fact. However, the theoretically possible fourth compound, the unsymmetrical 3,4-dimethyl-6-phenylazoaminobenzene was not found in the reaction mixture. This may be explained by the fact that when an unsubstituted para position is present on one of the possible azo components, the formation of the unsymmetrical *p*-aminoazo dye (III) will be more probable than that of the corresponding ortho substituted aminoazo compound, since the rearrangement will proceed at the position with the highest electron density. The structure of 3,4-dimethyl-4'-aminoazobenzene (III) was shown by destructive hydro-



-triazen] were unsuccessful [3]. Hydrogenation of 3,4-dimethyl-6-(4'-tolylazo)-aminobenzene (VI) led to *p*-toluidine and 4,5-diamino-1,2-xylene. The absorption spectrum of compound (VI) (λ_{\max} 327 and 437 $m\mu$) corresponded to that of an *o*-aminoazo compound (Fig. 2), which indicates the structure of this substance. The main reaction product from the rearrangement of the unsymmetrical triazen (V) in 3,4-dimethylaniline, was the symmetrical *o*-aminoazo dye (IV), obtained with a yield of 70.5%.

On rearranging 1-(3',4',5'-trimethylphenyl)-3-(3'',4''-dimethylphenyl)-triazene (VII) in 3,4-dimethylaniline, unsym. 3,4,5-trimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (VIII) was obtained with a yield of 80%; the structure of this follows indisputably from the method of its formation, its absorption spectrum (λ_{\max} 383 and 446 $m\mu$) which corresponds to that of an *o*-aminoazo compound, and the production of 3,4-dimethylaniline from it by reduction. On rearranging the triazen (VII) in 3,4,5-trimethylaniline 3,4,5-trimethyl-6-(3',4',5'-trimethylphenylazo)-aminobenzene (IX) was obtained with a yield of 90%; its structure follows from its method of formation, its elementary analysis, and its absorption spectrum (λ_{\max} 340 and 442 $m\mu$), which also corresponds to that of an *o*-aminoazo compound (Fig. 2).

It follows from a consideration of the known facts and the results obtained on the mechanism of the so-called diazoamino-aminoazo rearrangement that the conversion of unsymmetrical triazens into symmetrical aminoazo compounds consists of two independent rearrangements – the triazen rearrangement (the exchange of one azo component of the triazen with the amine of the medium) and the aminoazo rearrangement (rearrangement of the triazen into the aminoazo compound of the corresponding structure). The triazen rearrangement is catalyzed by protons. Confirmation of the presence of the independent rearrangement of one triazen into another may be found in the facts of the conversion of 1,3-diphenyltriazene into 1-phenyl-3-(4'-tolyl)-triazene and of 1,3-(2',4',5'-trimethylphenyl)-triazene into 1,3-di-(4'-tolyl)-triazene in *p*-toluidine [3]. The triazen rearrangement of unsymmetrical triazens does not take place, or is retarded, in the presence of the aromatic amine least alkylated in the nucleus; consequently, the subsequent aminoazo rearrangement of the unsymmetrical triazens leads to the production of the corresponding unsymmetrical para- or ortho-aminoazo dye in which the most highly alkylated component forms the azo constituent and the least alkylated component the diazo constituent. In the presence of the aromatic amine with the greatest degree of alkylation in the ring, an unsymmetrical triazen undergoes the triazen rearrangement into the symmetrical triazen and only the latter gives the symmetrical *o*-aminoazo dye corresponding to the amine of the medium as a result of the aminoazo rearrangement. An example of the rearrangement of unsym. 1-phenyl-3-(4'-tolyl)-triazene in *p*-toluidine is known from the literature; it led to the production of sym. 4-methyl-6-(4'-tolylazo)-aminobenzene [3], which is in agreement with the assumption expressed on the mechanism of the reaction.

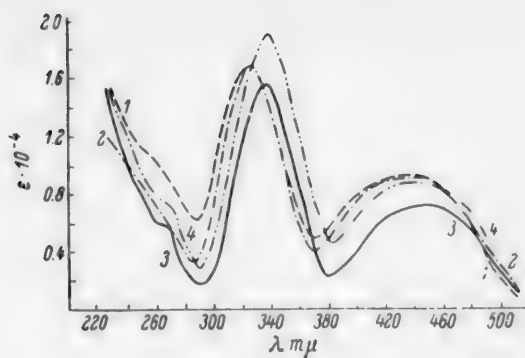


Figure 2. Absorption spectra (in alcohol). 1) 3,4-dimethyl-6-(4'-tolylazo)-aminobenzene (VI), 2) 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV), 3) 3,4,5-trimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (VIII), 4) 3,4,5-trimethyl-6-(3',4',5'-trimethylphenylazo)-aminobenzene (IX).

ing up to the present time, no satisfactory explanation can be given for the fact that the direct azo coupling of aniline with a benzene diazonium compound in the nucleus takes place with difficulty and only under special conditions [4], while the aminoazo rearrangement of 1,3-diphenyltriazene into 4-aminoazobenzene proceeds almost quantitatively. Consequently, the theory of the rearrangement of triazenes into aminoazo compounds which specifies the decomposition of the triazen into a diazonium salt and an aromatic amine with subsequent azo addition in the nucleus cannot give a satisfactory explanation of the facts obtained by us.

EXPERIMENTAL

A. Unsymmetrical triazenes. Azo coupling. A solution of 0.1 g-mole of an aromatic amine in a mixture of 20 ml of hydrochloric acid ($d_{40} 1.19$) and 180 ml of water at $65-80^\circ$ was cooled to $20-25^\circ$ and a solution of the diazonium salt prepared in the usual way from 0.1 g-mole of an aromatic amine, 20 ml of concentrated hydrochloric acid, and 0.1 g-mole of sodium nitrite, was added. Then 30 ml of 28% sodium acetate was added rapidly. After 2 hours, the precipitate was filtered off, washed with water, and dried.

1-(3',4'-dimethylphenyl)-3-phenyltriazene (I). From 12.2 g (0.1 g-mole) of 3,4-dimethylaniline (azo component) and 9.3 g (0.1 g-mole) of aniline (diazo component), 22.1 g (97.5%) of the triazen (I) was obtained in the form of yellowish elongated plates with m.p. $95.8-96.1^\circ$ (with decomp., from alcohol).

Absorption spectrum (in alcohol): λ_{\max} 239 mμ ($\epsilon 1.87 \cdot 10^4$) and 356 mμ ($\epsilon 2.20 \cdot 10^4$).

Found %: C 74.46, 74.59; H 6.88, 6.82; N 18.65, 18.56. $C_{14}H_{15}N_3$. Calculated %: C 74.63; H 6.70; N 18.65.

1-(3',4'-Dimethylphenyl)-3-(4"-tolyl)-triazene (V). From 12.1 g (0.1 g-mole) of 3,4-dimethylaniline (azo constituent) and 10.7 g (0.1 g-mole) of *p*-toluidine (diazo constituent), 22.65 g (96.5%) of the triazen (V) was obtained in the form of yellowish plates with m.p. $111-112^\circ$ (with decomp., from alcohol).

Absorption spectrum (in alcohol): λ_{\max} 241 mμ ($\epsilon 1.01 \cdot 10^4$) and 361 mμ ($\epsilon 1.13 \cdot 10^4$).

Found %: C 75.17, 75.04; H 7.32, 7.29; N 17.52, 17.48. $C_{15}H_{17}N_3$. Calculated %: C 75.80; H 7.10; N 17.48.

1-(3',4',5'-Trimethylphenyl)-3-(3',4'-dimethylphenyl)-triazene (VII). From 1.35 g (0.01 g-mole) of 3,4,5-trimethylaniline (azo constituent) and 1.21 g (0.01 g-mole) of 3,4-dimethylaniline (diazo constituent), 2.4 g (90%) of the triazen (VII) was obtained in the form of yellow prisms with m.p. $110.5-111.5^\circ$ (with decomp., from alcohol).

Absorption spectrum (in alcohol): λ_{\max} 244 mμ ($\epsilon 1.78 \cdot 10^4$) and 362 mμ ($\epsilon 2.11 \cdot 10^4$).

Found %: C 76.40, 76.54; H 8.12, 8.02; N 15.86, 15.98. $C_{17}H_{21}N_3$. Calculated %: C 76.36; H 7.92; N 15.71.

B. Rearrangement of unsymmetrical triazenes into aminoazo compounds. To a melt of 20 g of the aromatic amine (containing 1.25 g of the hydrochloride) was added 10 g of the triazen. The mixture was stirred for 3 hours at

35°, 3 hours at 40-45°, 3 hours at 50-60°, and 1 hour at 70°. The precipitate of azo dye which separated was filtered off and washed with alcohol (3 × 10 ml).

Rearrangement of 1-(3',4'-dimethylphenyl)-3-phenyltriazene (I). (a) In 3,4-dimethylaniline. From 10 g of the triazen (I) was obtained 6.8 g (60.5%) of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) as golden orange plates with m.p. 184.7-185.6° (from alcohol). A mixed melting point test with a substance obtained by the rearrangement of the corresponding symmetrical triazen [2] gave no depression of the melting point.

Found %: C 76.08, 75.71; H 7.88, 7.87; N 16.54, 16.42. $C_{16}H_{19}N_3$. Calculated %: C 75.85; H 7.56; N 16.58.

(b) In aniline. From 10 g of the triazen (I) was obtained 1.44 g (14.4%) of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) in the form of orange plates with m.p. 183-185° (from alcohol). It gave no depression of the melting point in admixture with a sample of the *o*-aminoazo compound (IV) obtained above.

Found %: C 75.86, 75.74; H 7.70, 7.68; N 16.63, 16.47. $C_{16}H_{19}N_3$. Calculated %: C 75.85; H 7.56; N 16.58.

Aniline was distilled with steam (at pH 8) from the mother liquors after the removal of the *o*-aminoazo compound (IV). Filtration of the residue gave 8.5 g of a substance from which, by fractional crystallization from alcohol, were isolated 4-aminoazobenzene (in the form of orange yellow crystals with m.p. 123-124° giving no depression of the melting point in admixture with a known sample) and 3,4-dimethyl-4'-aminoazobenzene (III) (dark orange prisms with m.p. 128.5-129.5°).

Absorption spectrum (in alcohol): λ_{\max} 247 m μ (ϵ 1.30 · 10⁴) and 385 m μ (ϵ 2.48 · 10⁴).

Found %: C 74.79, 74.47; H 6.66, 6.65; N 18.79, 18.44. $C_{14}H_{15}N_3$. Calculated %: C 74.63; H 6.70; N 18.65.

Hydrogenation of 4 g of 3,4-dimethyl-4'-aminoazobenzene (III) was carried out in 30 ml of alcohol in the presence of 3 g of a skeletal nickel catalyst for 2 hours at 60 atm. and 70-90°; after distilling off the solvent (pH of the medium 2), steam distillation at pH 8-9 gave 0.6 g (28%) of 3,4-dimethylaniline with m.p. 48-50°, giving no depression in a mixed melting point test with a known sample. The residue after distillation was evaporated to 40 ml. Filtration gave 1 g (52%) of *p*-phenylenediamine with m.p. 136-138° (from water) not giving a depression in the melting point with a known sample.

Rearrangement of 1-(3',4'-dimethylphenyl)-3-(4"-tolyl)-triazene (V). (a) In 3,4-dimethylaniline. From 10 g of the triazen (V) was obtained 7.5 g (70.5%) of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) in the form of golden orange plates with m.p. 184-185° from alcohol.

(b) In *p*-toluidene. From 20 g of the triazen (V) was obtained 18 g of a mixture of aminoazo compounds. Fractional crystallization yielded 4.5 g (22.5%) of 3,4-dimethyl-6-(4'-tolylazo)-aminobenzene (VI) as orange prisms with m.p. 158-159.5° (from alcohol).

Absorption spectrum (in alcohol): λ_{\max} 327 m μ (ϵ 1.69 · 10⁴) and 438 m μ (ϵ 0.94 · 10⁴).

Found %: C 75.26, 75.37; H 7.42, 7.35; N 17.48, 17.50. $C_{15}H_{17}N_3$. Calculated %: C 75.50; H 7.10; N 17.50.

Hydrogenation of 2 g of the *o*-aminoazo compound (VI) was carried out as above in 30 ml of alcohol with 1 g of catalyst; 0.25 g (29.5%) of *p*-toluidine distilled over with steam. *p*-Acetanilide (0.25 g) with m.p. 148-150° (from water), not giving any depression in the mixed melting point test with a known sample, was obtained from 0.2 g of the substance and 0.3 ml of acetic anhydride. The residue after the distillation of the *p*-toluidine yielded 0.75 g (65.2%) of 4,5-diamino-1,2-xylene with m.p. 127-128°, giving no depression of the melting point in admixture with a known sample.

Rearrangement of 1-(3',4',5'-trimethylphenyl)-3-(3",4"-dimethylphenyl)-triazene (VII). (a) In 3,4-dimethylaniline. From 1 g of the triazen (VII) was obtained 0.8 g (80%) of 3,4,5-trimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (VIII) as orange prisms with m.p. 158-159° (from alcohol). The substance gave a depression of the melting point in admixture with the substance (IX).

Absorption spectrum (in alcohol): λ_{\max} 338 m μ (ϵ 1.56 · 10⁴) and 446 m μ (ϵ 0.75 · 10⁴).

Found %: C 76.51, 76.23; H 8.27, 8.11; N 15.49, 15.75. $C_{17}H_{21}N_3$. Calculated %: C 76.36; H 7.92; N 15.71.

Hydrogenation of 0.3 g of the *o*-aminoazo compound (VIII) was carried out as above; distillation gave 0.06 g of 3,4-dimethylaniline with m.p. 47-49°, giving no depression of the melting point in admixture with a known sample.

(b) In 3,4,5-trimethylaniline. From 1 g of the triazen (VII) was obtained 0.5 g (90%) of 3,4,5-trimethyl-6-(3',4',5'-trimethylphenylazo)-aminobenzene (IX) as orange red plates with m.p. 169-170.8° (from alcohol).

Absorption spectrum (in alcohol): λ_{\max} 340 m μ (ϵ $1.90 \cdot 10^4$) and 442 m μ (ϵ $0.90 \cdot 10^4$).

Found %: C 76.63, 76.85; H 8.47, 8.36; N 14.93, 15.14. $C_{18}H_{23}N_3$. Calculated %: C 76.82; H 8.23; N 14.93.

SUMMARY

1. In many cases the diazoamino-aminoazo rearrangement must be considered as consisting of a triazen rearrangement and an aminoazo rearrangement.

2. It has been shown that the rearrangement of unsymmetrical triazens with the para position substituted by alkyl substituents in a medium consisting of the amine correspond to the most highly alkylated component of the triazen leads to symmetrical *o*-aminoazo compounds.

3. It has been found that unsymmetrical triazens with one substituted para position in a medium consisting of an amine also with a free para position, under appropriate conditions, exhibit a tendency to rearrange into *p*-aminoazo dyes.

4. In the rearrangement of unsymmetrical aromatic triazens with substituted para positions, the unsymmetrical *o*-aminoazo compounds corresponding to the components of the initial triazen are obtained in the first place.

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AN INVESTIGATION IN THE ALLOXAZINE AND ISOALLOXAZINE SERIES

II. A NEW SYNTHESIS OF COMPOUNDS OF THE ALLOXAZINE SERIES*

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Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 8,

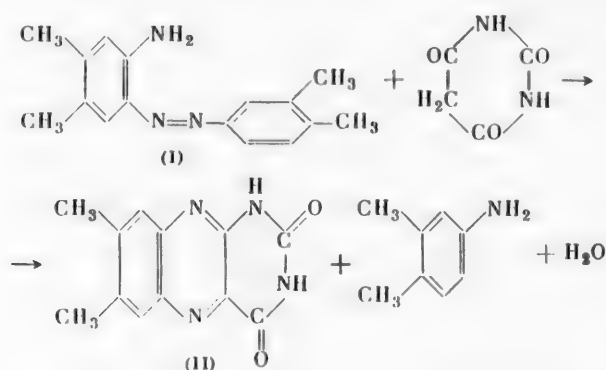
pp. 2779-2782, August, 1961

Original article submitted August 2, 1960

Until recently, alloxazines were obtained by condensing primary aromatic *o*-diamines with alloxan [2, 3] or with 5-halogeno- or 5,5-dihalogeno- barbituric acids [4], or by condensing primary aromatic *o*-diamines with 5-iso-nitrosobarbituric acid [5, 6].

It was of interest to obtain compounds of the alloxazine series by condensing primary aromatic *o*-aminoazo compounds with barbituric acid, which makes possible the directed production of a compound with a definite structure, while the method of producing alloxazines from primary aromatic *o*-diamines and alloxan frequently leads to a mixture of substances. The condensation of *o*-aminoazo compounds with substances containing carbonyl and active methylene groups was first proposed by Crippa [7] for the production of imidazoles and naphthopyrazines, and was then used by Tishler [8] for the synthesis of isoalloxazines, for example, the synthesis of riboflavine, by the condensation of secondary aminoazo compounds with barbituric acid, and was extended by us [9] and other authors [10] for the production of some other isoalloxazines.

From 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I) and barbituric acid by the new method we have synthesized natural lumichrome (II), a compound formed from riboflavine by the action of radiant energy on it [11].



3,4-Dimethylaniline was obtained from the reaction mixture after the isolation of the lumichrome (II), which is an indication that the condensation of primary *o*-aminoazo compounds with barbituric acid takes place through the reaction of the azo group with the active hydrogen atoms of the methylene group of the barbituric acid, leading to the rupture of the -N = N- bond and the formation of a primary amine and a new >C = N- bond. A reaction between the primary amino group of the *o*-aminoazo compound and one of the carbonyl groups of the barbituric acid adjacent to the methylene group takes place at the same time, with the elimination of a molecule of water and the formation of a new >C = N- bond of the pyrazine ring.

The structure of lumichrome (II) is shown by the complete agreement of its properties with the properties of 6,7-dimethylalloxazine which we obtained by a known method [3] from 4,5-dimethyl-1,2-diaminobenzene and allox-

* Communication 1 (see [1]).

an; by the absorption band in the infrared spectrum (in 1 N sodium carbonate) with λ_{\max} 260 and 350 m μ , which corresponds to lumichrome [3], and also by the results of paper chromatography, which gave a single spot with R_f 0.72 (butanol-acetic acid-water) with a characteristic bluish white fluorescence in ultraviolet light [11].

The condensation of aromatic *o*-aminoazo compounds with barbituric acid is catalyzed by acetic and oxalic acids (increasing the yield of lumichrome from 70 to 83.5%). To obtain the optimum yield of lumichrome, it is necessary to use the barbituric acid in 60% excess; with equimolecular ratios of the reagents, the yield is considerably lower (57%).

We also obtained lumichrome (II) from 3,4-dimethyl-6-(4'-tolylazo)-aminobenzene. From 4-methyl-6-(4'-tolylazo)-aminobenzene and barbituric acid by the same method, we synthesized 6-methylalloxazine, (one of the first compounds of the alloxazine series obtained by Kühling [12]) in admixture with 7-methylalloxazine by condensing 3,4-diaminotoluene hydrochloride with alloxan. We also showed that primary *o*-aminoazo compounds with a methyl group in position 5, for example, 3,4,5-trimethyl-6-(3',4',5'-trimethylphenylazo)-aminobenzene, do not condense with barbituric acid with an appreciable yield of alloxazine under the usual reaction conditions.

EXPERIMENTAL

6,7-Dimethylalloxazine (lumichrome) (II). A mixture of 5 g of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I) [13], 4.1 g of barbituric acid, 50 ml of *n*-butyl alcohol, and 10 ml of glacial acetic acid was heated to boiling for 4 hours. The yellow precipitate which separated was filtered off and washed with 10 ml of alcohol and boiling water (2 \times 20 ml). The product (5.2 g) was 77% lumichrome (determined by the spectrophotometric method in alcohol at λ_{\max} 250 m μ). The yield of lumichrome was 83.5%. After recrystallization from glacial acetic acid (1 : 110) it formed lemon yellow needles with m.p. above 320°.

Absorption spectrum (in alcohol): λ_{\max} 219 m μ (ϵ $2.76 \cdot 10^4$), 250 m μ (ϵ $2.95 \cdot 10^4$), 338 m μ (ϵ $0.8 \cdot 10^4$), and 385 m μ (ϵ $0.74 \cdot 10^4$); in 1 N sodium carbonate solution: λ_{\max} 260 m μ (ϵ $2.95 \cdot 10^4$) and 350 m μ (ϵ $0.63 \cdot 10^4$).

R_f 0.72 in *n*-butyl alcohol-acetic acid-water at a ratio of 4 : 1 : 5; type "M" paper. According to data in the literature [14], the R_f is 0.69.

The substance is sparingly soluble in methyl alcohol with a bluish white fluorescence in ultraviolet light.

Found %: C 59.37, 59.30; H 4.24, 4.25; N 23.34, 23.18. $C_{12}H_{10}O_2N_4$. Calculated %: C 59.49; H 4.16; N 23.13.

The solvent was distilled off from the mother liquors (at pH 2) and then the aromatic amine was steam distilled (at pH 9). A yield of 1.05 g (43.5%) of 3,4-dimethylaniline with m.p. 49-50° was obtained; the substance gives no depression of the melting point in admixture with a known sample.

Lumichrome was obtained in a yield 90% from 3,4-dimethyl-6-(4'-tolylazo)-aminobenzene [15].

6-Methylalloxazine. 6-Methylalloxazine (yield 88%) was obtained in the form of lemon yellow crystals with m.p. above 320° (from glacial acetic acid) from 5 g of 4-methyl-6-(4'-tolylazo)-aminobenzene and 3.25 g of barbituric acid by the same method of condensation. The substance has a bluish green fluorescence in ultraviolet light (in water).

Absorption spectrum (in 1 N sodium carbonate solution): λ_{\max} 260 m μ (ϵ $1.35 \cdot 10^4$) and 330 m μ (ϵ $0.24 \cdot 10^4$).

Found %: C 57.90, 57.65; H 3.77, 3.56; N 24.76, 24.48. $C_{11}H_8O_2N_4$. Calculated %: C 57.89; H 3.53; N 24.55.

SUMMARY

1. A new synthesis of compounds of the alloxazine series has been accomplished by the condensation of primary *o*-aminoazo compounds with barbituric acid.
2. The reaction between primary *o*-aminoazo compounds and barbituric acid is catalyzed by organic acids (acetic, oxalic, etc.).

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CHROMATOGRAPHIC AND ELECTROPHORETIC INVESTIGATION OF THE FORMATION OF FOLIC ACID AND SOME SIMPLE PTERIDINES

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One of the methods for the synthetic production of folic acid (I) consists in the three-component condensation of 2,4,5-triamino-6-hydroxypyrimidine (II), 2,3-dibromopropionaldehyde (III), and *p*-aminobenzoylglutamic acid (IV) [1]. This reaction does not proceed unambiguously and results in the formation of a difficultly separable mixture containing only 25-30% of folic acid together with other substances of the nature of pteridines.

In spite of the fact that the 4- and 5-amino groups in 2,4,5-triamino-6-hydroxypyrimidine possess different reactivities, there is always the known probability of the formation of isomeric pteridines in those cases where an unsymmetrically constructed three-carbon component is used for the condensation. Thus, on condensing the dihydrochloride or sulfate of 2,4,5-triamino-6-hydroxypyrimidine (II) with 2,3-dibromopropionaldehyde (III) in a mineral acid, 7-methylpteridine [2] was obtained, while at pH 4, 6-methylpteridine was obtained. According to other data [3], the condensation of the same substances in an acetate buffer at pH 7-8 leads to the formation of 6-hydroxymethylpteridine contaminated with 7-methylpteridine.

As is well known, many pteridines do not possess sharp melting points and cannot be recrystallized from organic solvents. Therefore, for example, to identify the isomeric methylpteridines, they are oxidized to the corresponding carboxylic acids and the absorption spectra of the latter in the ultraviolet region are examined. However, there are contradictory data for the maximum absorption of pteridine-7-carboxylic acid: 392 [2] and 325 m μ [4]. Paper chromatography has also been used for the separation of the isomeric pteridine-6- and pteridine-7-carboxylic acids obtained by oxidation of the corresponding methylpteridines [5]. Nevertheless the use of oxidation methods for the clear identification of the simple pteridines presents considerable difficulties.

An investigation of the structure of the compounds formed in the three-component condensation in the synthesis of folic acid enables conclusions to be drawn on the mechanism of this complex and ambiguously-proceeding reaction. For this purpose, we used the methods of paper chromatography and electrophoresis to identify the substances formed in the condensation.

The known methods for detecting folic acid on a chromatogram are characterized by considerable cumbrousness [4, 6, 7]. Therefore we detected it by a simple method consisting in treating the paper strip with a 0.03-0.05% KMnO₄ solution and drying it in a current of air at room temperature; the folic acid was detected in ultraviolet radiation by the blue-fluorescing spot of pteridine-6-carboxylic acid formed from it. It is possible to detect 2-4 γ of folic acid in this way.

On investigating a mixture of the unpurified substances obtained by the three-component condensation by paper chromatography [solvent: butanol-acetic acid-water (4 : 1 : 5)], folic acid was found together with a number of spots possessing a weak blue fluorescence (Fig. 1, sample 1).

To identify these spots, reference materials were placed on the chromatogram at the same time: 6-methylpteridine (VII) (Fig. 1, sample 3), obtained by the reduction of folic acid with zinc in hydrochloric acid; 7-methylpteridine (IX) (samples 4 and 5) and 6-hydroxymethylpteridine (X) (sample 6), obtained by repeating syntheses described in the literature. It was found that, in the sample of the mixture of substances under investigation (sample 1), besides by the spot with R_f 0.17 identified as folic acid (I) (corresponding to sample 2), there were two intense spots, which were identified as: 6-hydroxymethylpteridine (R_f 0.28) and 6-methylpteridine (R_f 0.36). Comparison of the R_f values of samples of 7-methylpteridine (XI) obtained by the condensation of 2,4,5-triamino-6-hydroxypyrimidine

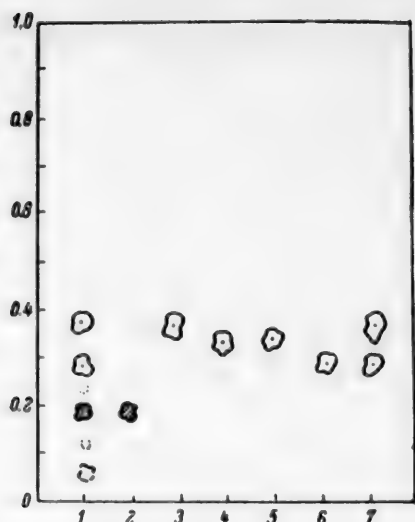


Fig. 1. Chromatogram of folic acid and pteridines; 1) mixture of substances (folic acid and pteridines) obtained by the interaction of (II), (III), and (IV) at pH 3-4; 2) folic acid (I); 3) 6-methylpteridine (IV) from folic acid; 4) 7-methylpteridine (XI) from (II) and (III) at pH 1; 5) 7-methylpteridine (XI) from (II) and bromoacetone; 6) 6-hydroxymethylpteridine (X) from (II) and (III) at pH 7-8; 7) 6-hydroxymethylpteridine (X) and 6-methylpteridine (VII) from (II) and (III) at pH 3-4. Solvent: butanol-acetic acid-water (4 : 1 : 5).

with 2,3-dibromopropionaldehyde at pH 1 [2] (sample 4) or with bromoacetone [3] (sample 5) with the value of R_f for 6-methylpteridine (VII) enables these two isomers to be separated on the basis of the difference in their partition coefficients, particularly after 2- and 3-fold chromatography. No 7-methylpteridine was found in the mixture of substances obtained from the three component condensation (Fig. 1, sample 1). In addition to the identified spots on the chromatogram of unpurified folic acid, 2-3 other insignificant spots were observed, no detailed investigation of which was carried out.

Since the methylpteridines possess similar R_f values and are separated in only one of the systems of solvents which we investigated, to obtain a clear identification, we compared their electrophoretic mobility on paper. It was found that, under the conditions of the experiment, 7-methylpteridine does not move from the starting line while 6-methylpteridine migrates towards the anode (Fig. 2). 6-Hydroxymethylpteridine and folic acid possess approximately equal mobilities and the position of their spot differs markedly from the 7-methylpteridine spot. It was shown by the electrophoretic method that there is no 7-methylpteridine in the mixture under investigation, since no fluorescent spot was found at the starting point.

Thus, it has been shown from the results of electrophoretic investigation and chromatographic identification and established the basis of analysis by chromatographic and fluorimetric methods that in the three-component condensation at pH 3-4, besides folic acid (25-30%) 6-methylpteridine (20-25%) and 6-hydroxymethylpteridine (about 25%) are formed and that, which is important to note, 7-methylpteridine is not found among the reaction products.

These results give grounds for supposing that the three-component condensation with the formation of folic acid and other substances goes through a series of successive reactions. Initially the condensation of 2,4,5-triamino-6-hydroxypyrimidine (II) with 2,3-dibromopropionalde-

hyde (III) leads to 5,6-dihydro-6-bromomethylpteridine (V), which, under the conditions of the reaction, undergoes a series of subsequent conversions:

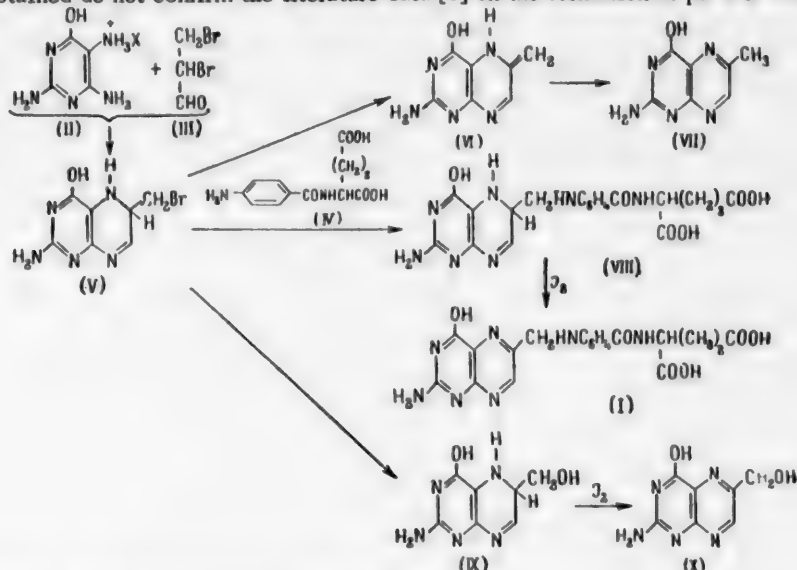
- Dehydrobromination of (V) and subsequent isomerization of the extra-cyclic double bond of the intermediate compound (VI) lead to 6-methylpteridine (VII);
- The reaction of (V) with *p*-aminobenzoylglutamic acid (IV) leads to dihydrofolic acid (VIII), dehydrogenation of which with iodine gives folic acid (I); and
- Hydrolysis of compound (V) and subsequent dehydrogenation of compound (IX) gives 6-hydroxymethylpteridine (X).

R_f Values in the Chromatography of Pteridines

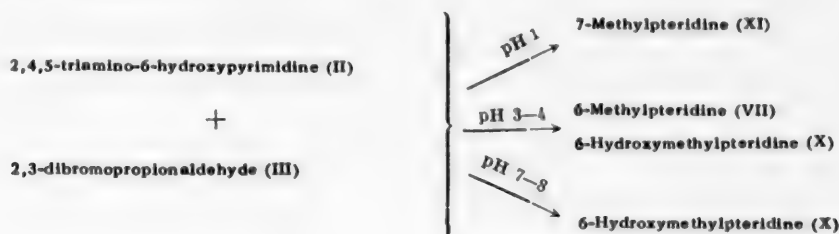
Substance	Solvent			
	1	2	3	4
Folic acid (I)	0.17	0.18	0.00	0.71
7-Methylpteridine (XI)	0.32	0.55	0.11	0.77
6-Methylpteridine (VII)	0.36	0.57	0.10	0.74
6-Hydroxymethylpteridine (X)	0.28	0.51	0.08	0.72

Note. Solvents: No. 1) butanol-acetic acid-water (4 : 1 : 5); No. 2) pyridine-butanol-acetic acid-water (10 : 7.5 : 1.5 : 6); No. 3) butanol saturated with water; No. 4) isopropylalcohol-formic acid-water (4 : 1 : 5).

The observation that the crude condensation product contains halogen and that its additional treatment with *p*-aminobenzoylglutamic acid leads to an increased yield of folic acid [8] is in agreement with the above scheme. Confirmation of the mechanism of this complex reaction may be found in the fact that the condensation of 2,4,5-triamino-6-hydroxypyrimidine (II) with 2,3-dibromopropionaldehyde (III) at pH 4, i.e. just under those conditions which are used for the three-component condensation with the participation of *p*-aminobenzoylglutamic acid, leads to a mixture of 6-methylpteridine (VII) and 6-hydroxymethylpteridine (X) (Fig. 1, sample 7), in contrast to reference [2] in which only 6-methylpteridine was obtained at pH 4. Compound (X) (spot with R_f 0.28) was identified with 6-hydroxymethylpteridine (sample 6) obtained by the condensation of the same starting materials at pH 8 [3]. The chromatographic results which we obtained do not confirm the literature data [3] on the formation at pH 8 of 7-methylpteridine as well.



R_f 0.28) was identified with 6-hydroxymethylpteridine (sample 6) obtained by the condensation of the same starting materials at pH 8 [3]. The chromatographic results which we obtained do not confirm the literature data [3] on the formation at pH 8 of 7-methylpteridine as well.



EXPERIMENTAL

The pteridines were synthesized in the following ways: 6-methylpteridine according to the directions of reference [2]; 6-hydroxymethylpteridine according to the data of reference [3]; and 7-methylpteridine according to the data of references [2, 3]. Folic acid was synthesized according to the data of reference [1] — by the addition of solution of 2,3-dibromopropionaldehyde in isopropyl alcohol and a solution of iodine in potassium iodide at pH 3-4 to a solution of the dihydrochloride of 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoylglutamic acid in aqueous isopropyl alcohol (with vigorous stirring). The solid mixture of substances formed was separated and dried. The mixture of substances obtained as a result of the three-component condensation, and the simple pteridines, were chromatographed by the method of downward chromatography; "Leningrad M" chromatographic paper, density 85, was used, (see Table 1 and Fig. 1).

The simple pteridines synthesized possess fluorescence spectra with a maximum at 477 $m\mu$. Hence, for the semi-quantitative determination of them in a mixture, the spots of these substances separated on a chromatogram were cut out and eluted with 0.1 N NaOH and the fluorescence of the solutions obtained was then measured and compared with the values of standard samples of eluates of spots with known amounts of methylpteridine and hydroxymethylpteridine.

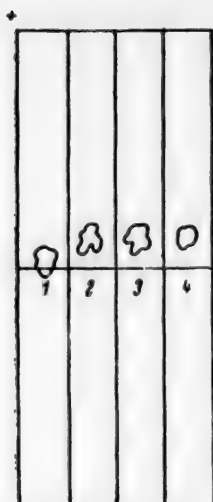


Fig. 2. Paper electrophoresis. 1) 7-methylpteridine (XI); 2) 6-methylpteridine (VII); 3) mixture after three-component condensation; 4) 6-hydroxymethylpteridine (X). Phosphate buffer 1/15 M, pH 9.2, 200 V, 7 hours.

An ÉFA-1 apparatus was used for the electrophoretic investigations. The samples to be analyzed, in 0.1 N NaOH were applied to the middle of a strip of paper 4 cm wide and after impregnation with a 1/15 M solution of Na_2HPO_4 (pH 9.2) electrophoresis against this buffer solution was carried out at 250 V for 7 hours. After the end of the process, the paper strips were dried at room temperature and the distribution of the pteridines and folic acid was determined by the above-described methods (Fig. 2).

SUMMARY

1. It has been shown by the methods of paper chromatographic and electrophoretic separation that, as in the two-component condensation of 2,4,5-triamino-6-hydroxypyrimidine and 2,3-dibromopropionaldehyde, 6-methyl- and 6-hydroxymethylpteridines are formed - together with folic acid - in the condensation of 2,4,5-triamino-6-hydroxypyrimidine, 2,3-dibromopropionaldehyde, and p-aminobenzoylglutamic acid at pH 3-4.

2. The condensation of 2,4,5-triamino-6-hydroxypyrimidine and 2,3-dibromopropionaldehyde at pH 8 gives only 6-hydroxymethylpteridine.

3. A simple method of showing up spots of folic acid on a chromatogram has been proposed.

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STUDY OF THE POLAROGRAPHIC AND ADSORPTION PROPERTIES OF BENZOYL DERIVATIVES OF SOME BARBITURATES

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It is known from the literature [1] that the attachment of a benzoyl radical to the nitrogen of some barbiturates (veronal, luminal, etc.) increases their anti-spasmodic action.

Zuman and Koryta have studied the polarographic properties of barbituric acid [2], veronal [3] and derivatives of thiobarbituric acid [4]. The object of the present work is the study of the polarographic and adsorption properties of some barbiturates and their benzoyl derivatives and an investigation of the possibility of establishing a connection between the polarographic and adsorption properties of these materials and their anti-spasmodic action.

EXPERIMENTAL

The polarographic study was carried out using a visual polarograph [5] in an H-form electrolyzer with a saturated calomel electrode as auxiliary electrode. The medium was a borate buffer with pH 9.2 [2]. The dissolved atmospheric oxygen was removed from the solution under investigation by a current of hydrogen.

The electrocapillary curves were studied by the method of drop counting. At each value of the potential, the dropping period of the dropping mercury electrode was determined. In order to convert the values of the dropping period obtained to the surface tension of the mercury in dyne/cm, an experiment was carried out in 1 N sodium sulfate at 25°. The surface tension of this solution and the maximum of the electrocapillary curve at 25° was taken as 426.7 dyne/cm [6]. As can be seen from the data of Table 1, under the conditions of our experiments the rate of flow of the mercury from the capillary does not depend on the potential [7].

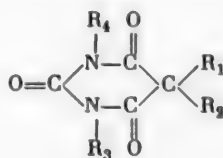
TABLE 1.

Potential relative to the saturated calomel electrode (in V)	+0.2	0.0	-0.2	-0.4	-0.6	-0.8	-1.0	-1.2
Rate of flow of the mercury (mg/sec.).	1.302	1.301	1.297	1.301	1.302	1.301	1.300	1.300

The suppression of the polarographic maximum at the first oxygen wave was studied in the polarographic electrolyzer with mercury on the bottom as auxiliary electrode. The point of intersection of the smooth curve (drawn through the polarographic maxima at various concentrations in solution of the substances under investigation) with the oxygen wave in a solution containing 0.01% of gelatine was taken as the diffusion current of the first oxygen wave (see Fig. 4).

Results of the Experiments and Discussion

The barbituric acid derivatives studied in the present investigation may be represented by the general formula:



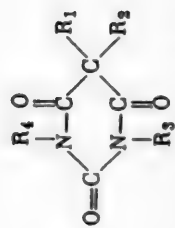


TABLE 2. Barbituric acid derivatives

Comp. No.	Name	R ₁	R ₂	R ₃	R ₄
(I)	Veronal	C ₂ H ₅	C ₂ H ₅	C ₂ H ₅	H
(II)	Benzoylveronal	C ₂ H ₅	C ₂ H ₅	COC ₆ H ₅	H
(III)	Luminal	C ₂ H ₅	C ₆ H ₅	C ₆ H ₅	H
(IV)	Benzoyluminal (benzonal)	C ₂ H ₅	C ₆ H ₅	COC ₆ H ₅	H
(V)	Barbamil	C ₂ H ₅	C ₆ H ₁₁	H	H
(VI)	Benzoylbarbamil	C ₂ H ₅	C ₆ H ₁₁	COC ₆ H ₅	H
(VII)	Barbital	CH ₃	$\begin{array}{c} \text{CH}-\text{CH}_2-\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{C} \quad \text{CH}_2 \\ \diagdown \quad \diagup \\ \text{CH}-\text{CH}_2-\text{CH}_2 \end{array}$	H	CH ₃
(VIII)	Benzoylbarbital	CH ₃	$\begin{array}{c} \text{CH}-\text{CH}_2-\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{C} \quad \text{CH}_2 \\ \diagdown \quad \diagup \\ \text{CH}-\text{CH}_2-\text{CH}_2 \end{array}$	COC ₆ H ₅	CH ₃
(IX)	Dibenzoylbarbamil	C ₂ H ₅	C ₆ H ₁₁	COC ₆ H ₅	COC ₆ H ₅
(X)	Diacetylsalicyluminal	C ₂ H ₅	C ₆ H ₅	COC ₆ H ₄ OCOCH ₃	COC ₆ H ₄ OCOCH ₃

Note. Substances (II), (IV), (VI), (VIII), (IX), and (X) were synthesized in L.P. Kulev's laboratory.

R_1 and R_2 are various hydrocarbon radicals; R_3 is hydrogen or a benzoyl group; and R_4 is hydrogen (in the majority of the compounds studied), or a methyl or benzoyl group. The names of the derivatives of barbituric acids studied and the nature of the substituents R_1 , R_2 , R_3 and R_4 in them are given in Table 2. This numeration of the compounds is preserved in all the figures and tables for simplicity and convenience. All potentials in the text, in the tables, and in the figures (except for Fig. 4) are given in volts relative to the saturated calomel electrode.

The results of the polarographic study of the barbituric acid derivatives listed in Table 2 are given in Table 3 and in Figs. 1 and 2. Of the 10 compounds studied, 6 (I-VI) give two anode waves. For barbital (VII) the first wave is lacking. Two compounds (VIII and IX) give no polarographic waves.

TABLE 3.

Comp. No.	Name	C_{lim} (in mole/l)	I_{lim} (in μA)	(in V)	(in V)	K_D^5
(I)	Veronal	0.12	0.180	-0.02	0.12	1.8
(II)	Benzolyveronal	—	0.185	0.09	— ⁶	— ⁶
(III)	Luminal	0.5	0.243	0.03	0.16	2.82
(IV)	Benzoylluminal (benzonal)	0.6	0.091	0.06	0.16	2.1
(V)	Barbamil	0.4	0.250	0.035	0.12	3.16
(VI)	Benzoylbarbamil	1.1	0.146	0.058	— ⁶	— ⁶
(VII)	Barbital	— ⁷	— ⁷	— ⁷	0.11	2.9

Notes.

¹ C_{lim} is the concentration at which a constant adsorption current is reached.

² I_{lim} is the constant adsorption current.

³First half-wave anode potential (more negative).

⁴Second half-wave anode potential.

⁵Diffusion current constant for the second wave.

⁶Second wave unclear because of its proximity to the initial rise of the polarogram.

⁷First (adsorption) wave absent.

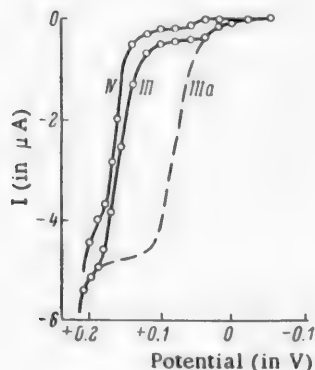


Fig. 1. Anode polarographic waves of 10^{-3} M solutions in borate buffer (pH 9.2). III - luminal; IV - benzoylluminal; IIIa - theoretical anode wave of luminal in the absence of adsorption of the oxidation product at the electrode.

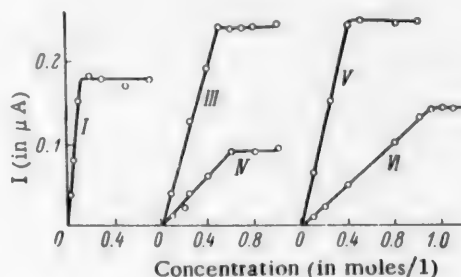


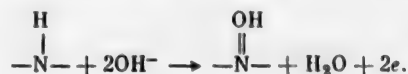
Fig. 2. Dependence of the height of the first anode (more negative) wave on the concentration of the organic compound. The numbers of the curves correspond to the serial numbers of the substances studied in Table 2.

We have shown that with all the six compounds studied by us which give two anode waves (I-VI), the first anode wave (the more negative, see Fig. 1) has an adsorption character. On increasing the concentration of the substance in the solution, the first anode wave began to rise proportional-

ly to the concentration and then reached a limiting value which no longer depended on the concentration (Fig. 2 and

Table 3). Under these circumstances, the second wave continued to grow proportionally to the concentration, i.e., the second wave is a diffusion wave.

We give a somewhat different explanation of the appearance of the adsorption wave from Zuman [4]. If adsorption of the oxidation product is absent then the luminal, for example, would give only one anode wave (see wave IIIa in Fig. 1). This anode wave may be represented by the following general equation for the anode process:



If the product of electrooxidation is strongly adsorbed, it rapidly accumulates on the surface of the mercury anode and the supply of the initial material from the solution begins to be hindered by the rate of penetration of the initial substance through this adsorption film. This mechanism of the effect of surface-active substances on electrode processes in the discharge of inorganic ions has been proposed and studied in a number of papers [8]. At sufficiently positive potentials, desorption of the organic molecules takes place on account of the electrostatic effect of the attraction of molecules of the dielectric (water) into the field of the electrical double layer at the mercury-solution boundary and the expulsion from the surface layer of the molecules of the organic compounds [9]. Then the supply of substance to the surface of the electrode increases and the height of the wave reaches the magnitude of the normal diffusion current (see Fig. 1).

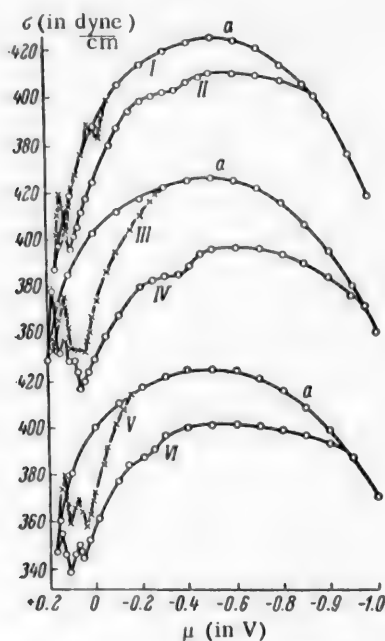


Fig. 3. Electrocapillary curves in 10^{-3} M solution of organic compounds in borate buffer (pH 9.2). The numbers of the curves correspond to the serial numbers of the substances in Table 2. Curve a is for a solution of borate buffer in the absence of an organic compound in the solution.

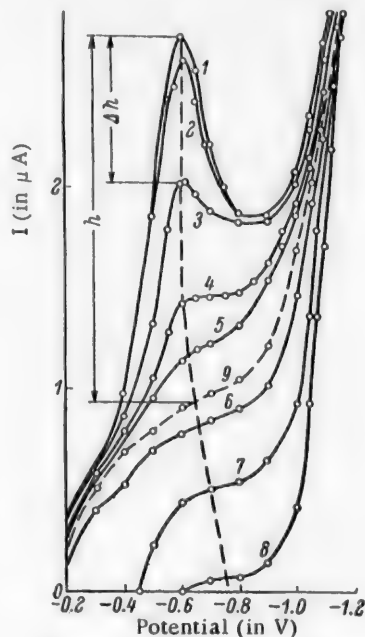


Fig. 4. Influence of the concentration of benzoylbarbamil on the height of the polarographic maximum of the first oxygen wave in borate buffer (pH 9.2). 1) 0, 2) 10^{-3} M, 3) 10^{-6} M, 4) $2.5 \cdot 10^{-6}$ M, 5) 10^{-5} M, 6) 10^{-4} M, 7) $2.5 \cdot 10^{-4}$ M, 8) 10^{-3} M, 9) 0.01% solution of gelatine (normal diffusion wave). Values of the potential given with respect to the mercury on the bottom.

The results of the investigation of the electrocapillary curves in solutions of barbituric acid derivatives are given in Fig. 3, from which it can be seen that the benzoyl derivatives are adsorbed considerably more strongly than the cor-

responding compounds without a benzoyl group (veronal, luminal, barbamil), which can easily be explained by the polarity of the benzoyl group.

Near the first anode half-wave potential (about +0.1 V with respect to the saturated calomel electrode; Fig. 3) a minimum in the surface tension connected with the adsorption of the product of electrooxidation of the given compound and with its subsequent desorption is observed. A second weaker minimum in the curves is located close to the second anode half-wave potential of the given compound.

Close to the maxima of the electrocapillary curves, a step is observed in the solutions of all three benzoyl derivatives (Fig. 3). This step can be explained by a change in the orientation of the dipolar molecules of these compounds in the surface layer connected with the overcharging of the double layer at the maximum of the electrocapillary curves.

Compounds (VIII), (IX), and (X) (see Table 2) give no polarographic waves and do not affect the shape of the electrocapillary curves.

The results of the investigation of the influence of the six compounds (I-VI) on the oxygen polarographic maximum are given in Figs. 4 and 5. In the plot of y against $\log c$ (Fig. 5), the experimental points in a definite range of concentrations ($\log c$ from -6 to -3) are satisfactorily located on straight lines intersecting at a single point for which $\log c = 7.1$ and $y = 0$. C is the concentration of the surface-active substance (in g-mole/l); $y = 100 \Delta h/h_0$ is the relative rise of the oxygen maximum (in percent); and h_0 is the height of the oxygen maximum without the surface-active substance in the solution. These six curves in Fig. 5 can be expressed by a single equation with one empirical constant b :

$$y = b(\log c - 7.1).$$

The values of the constant b for the six compounds studied are given in Table 4.

The values of y greater than 100% at high concentrations of the benzoyl derivatives (see Fig. 5) are explained by the fact that these compounds, being adsorbed on the surface, not only prevent the tangential movement of the mercury but also influence the kinetics of the electrode process of the electroreduction of oxygen. This leads to the situation that the height of the oxygen wave becomes lower than the value of the diffusion current (in the presence of 0.01% of gelatine) [7, 9].

TABLE 4.

Compound No. (see table 2)	(I)	(II)	(III)	(IV)	(V)	(VI)
Value of the constant b	15	33	26	40	23	37

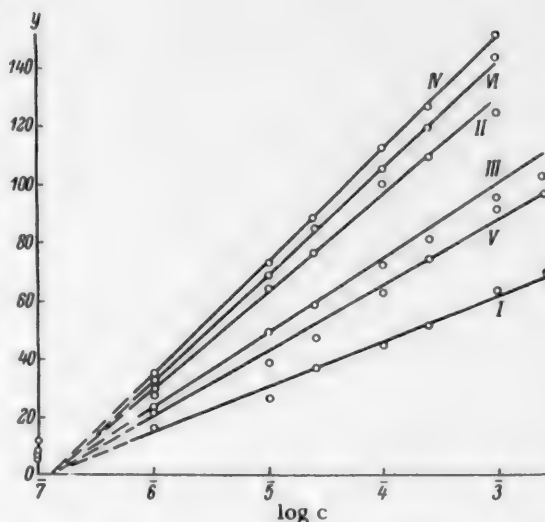


Fig. 5. Relative increase in the height of the oxygen maximum (y) in borate buffer (pH 9.2) as a function of the logarithm of the concentration of the organic compound in the solution. The numbers of the curves correspond to the serial numbers of the substances studied in Table 2.

Comparison of the polarographic and adsorption properties on the one hand, and the physiological action of the compounds studied on the other hand, leads to the conclusion that the polarographic properties of these compounds differ little from one another. The adsorption properties differ to a considerably greater extent. Benzonal (benzoylluminal, IV), which possesses the greatest anti-spasmodic action of the materials studied, also has the most pronounced adsorption properties. This is expressed by the fact that benzonal gives the lowest limiting adsorption polarographic wave (Table 3, Fig. 2), the highest increase in the surface tension at the maximum of the electrocapillary curve, and

the most negative desorption potential (Fig. 3), and also the greatest relative rise in the polarographic maximum at the first oxygen wave (Table 4, Fig. 5). Consequently, the anti-spasmodic action in the series of barbiturates studied depends fundamentally on the capacity of these compounds for being adsorbed. Thus, it is possible to expect that intensification of the adsorption properties on the introduction of new substituents into these compounds will also lead to an intensification of their anti-spasmodic action.

In conclusion, we express our deep gratitude to L.P. Kulev for supplying the organic compounds and for valuable observations in the discussion of the results obtained.

SUMMARY

1. A polarographic study of 10 derivatives of barbituric acid forming medical preparations with soporific and anti-spasmodic action has been carried out. It has been shown that the first anode wave observed with six of the compounds has an adsorption character.

2. The electrocapillary curves of the same 10 compounds have been studied. It has been shown that the six compounds giving anode polarographic waves reduce the surface tension considerably. The benzoyl derivatives reduce the surface tension of mercury to a greater extent and over a wider range of potentials than the other compounds.

3. The surface-active properties of the six compounds have been studied in respect of their influence on the polarographic maximum of the oxygen wave. It has been shown that, in the range of concentrations from 10^{-6} to 10^{-3} M, the relationship between the relative rise of the oxygen maximum and the logarithm of the concentration of the organic compounds has the form of straight lines intersecting at a single point. An empirical equation with a single constant depending on the nature of the compound has been put forward which can encompass all the experimental results on the influence of these compounds on the oxygen maximum.

4. A comparison of the polarographic and adsorption properties of the barbiturates studied with their anti-spasmodic action leads to the conclusion that there is a definite parallelism between the anti-spasmodic activity of these preparations and their adsorption properties.

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LETTERS TO THE EDITOR

THE CONVERSION OF 5-PHENYLPYRAZOLINE TO 3-PHENYLPYRAZOLINE

I. I. Grandberg

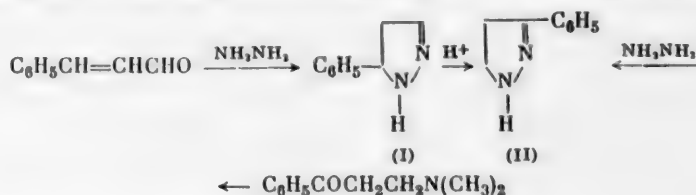
Moscow M.V. Lomonosov State University

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 8,

p. 2793, August, 1961

Original letter submitted April 19, 1961

It is considered to be rigidly established that pyrazolines do not possess tautomerism of the pyrazole type [1-3]. 5-Phenylpyrazoline (I) and 3-phenylpyrazoline (II) are obtained by different routes and have different constants



The present letter reports that 5-phenylpyrazoline, obtained from cinnamaldehyde (b.p. 138° at 12 mm; m.p. -30--20°; picrate, m.p. 180°; N-acetyl derivative, m.p. 53-54°), on heating to 150° with catalytic traces of strong acids is converted into 3-phenylpyrazoline (b.p. 157° at 12 mm; m.p. 45°; picrate, m.p. 153-154°; N-nitroso derivative, m.p. 154°; N-acetyl derivative, m.p. 138°).

All the derivatives give no depression of the melting points with the corresponding derivatives obtained from authentic 3-phenylpyrazoline.

A more detailed study of the isomerization of pyrazoline systems will form the subject of a special paper.

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CHLOROMETHYLATED 2-PYRONES

N.P. Shusherina, N.D. Dmitrieva and R.Ya. Levina

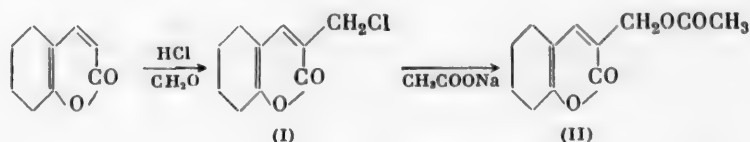
Moscow M.V. Lomonosov State University

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 8,

p. 2794, August, 1961

Original letter submitted April 13, 1961

Continuing the study of the reaction of an electrophilic substituent in the 2-pyrone series [1-3], we have carried out their chloromethylation for the first time, using 5,6-cyclohexano-2-pyrone. On passing a current of hydrogen chloride into a mixture of the 2-pyrone, formalin, and dichloroethane for 2 hours at 60-70°, a chloromethyl derivative of 5,6-cyclohexano-2-pyrone (I) was obtained in the form of an oil which resinified completely on distillation.



The presence of a chloromethyl group in compound (I) was shown by the production of a crystalline thiuronium picrate, with m.p. 193-194° (from alcohol, decomp.) which is characteristic for chloromethyl derivatives. The reaction of (I) with sodium acetate in glacial acetic acid, heating, yielded a crystalline acetate (II); yield 17%, calculated on the initial pyrone. M.p. 76.5-77.5° (from petroleum ether).

Found %: C 65.29, 65.16; H 6.41, 6.21. $\text{C}_{12}\text{H}_{14}\text{O}_4$. Calculated %: C 64.86; H 6.35.

The acetoxymethyl derivative of 5,6-cyclohexano-2-pyrone (II) obtained readily reacted with maleic anhydride, forming the double adduct characteristic for 2-pyrones, with m.p. 286-287° (from ethyl acetate, decomp.).

Found %: C 60.71, 60.94; H 4.87, 4.99. $\text{C}_{19}\text{H}_{18}\text{O}_8$. Calculated %: C 60.96; H 4.89.

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Soviet Journals Available in Cover-to-Cover Translation

ABBREVIATION	RUSSIAN TITLE	TITLE OF TRANSLATION	PUBLISHER	TRANSLATION BEGAN
				Vol. Issue Year
AÉ	Atomnaya énergiya	Soviet Journal of Atomic Energy	Consultants Bureau	1 1 1956
Akust. zh.	Akusticheskii zhurnal	Soviet Physics - Acoustics	American Institute of Physics	1 1 1955
Astr.(on). zh(urn).	Antibiotiki	Antibiotics	Consultants Bureau	1 1 1959
Avto(mak). svarka	Astronomicheskii zhurnal	Soviet Astronomy-AJ	American Institute of Physics	34 1 1957
	Avtomaticheskaya svarka	Automatic Welding	British Welding Research Association (London)	
	Avtomatika i Telemekhanika	Automation and Remote Control	Institution of Engineers and Electricians	1 1959
	Biofizika	Biophysics	Instrument Society of America	27 1 1956
	Biokhimiya	Biochemistry	National Institutes of Health*	1 1957
Byull. éksp(erim). biol. i med.	Byulleten' éksp(erim)ental'noi biologii i meditsiny	Bulletin of Experimental Biology and Medicine	Consultants Bureau	21 1 1956
DAN (SSSR)			Consultants Bureau	41 1 1959
Doklady AN SSSR	Doklady Akademii Nauk SSSR	The translation of this journal is published in sections, as follows:		
		Doklady Biochemistry Section	American Institute of Biological Sciences	106 1 1956
		Doklady Biological Sciences Sections (Includes: Anatomy, biophysics, cytology, ecology, embryology, endocrinology, evolutionary morphology, genetics, histology, hydrobiology, microbiology, morphology, parasitology, physiology, zoology sections)	American Institute of Biological Sciences	112 1 1957
		Doklady Botanical Sciences Sections (Includes: Botany, phytopathology, plant anatomy, plant ecology, plant embryology, plant physiology, plant morphology sections)		
		Proceedings of the Academy of Sciences of the USSR, Section: Chemical Technology	Consultants Bureau	106 1 1956
		Proceedings of the Academy of Sciences of the USSR, Section: Chemistry	Consultants Bureau	106 1 1956
		Proceedings of the Academy of Sciences of the USSR, Section: Physical Chemistry	Consultants Bureau	112 1 1957
		Doklady Earth Sciences Sections (Includes: Geochemistry, geology, geophysics, hydrogeology, mineralogy, paleontology, petrography, permafrost sections)	American Geological Institute	124 1 1959
		Proceedings of the Academy of Sciences of the USSR, Section: Geochemistry	Consultants Bureau	106- 1 1957- 1958
		Proceedings of the Academy of Sciences of the USSR, Section: Geology	Consultants Bureau	106- 1 1957- 1958
		Doklady Soviet Mathematics	The American Mathematics Society	131 1 1961
		(Includes: Aerodynamics, astronomy, crystallography, cybernetics and control theory, electrical engineering, energetics, fluid mechanics, heat engineering, hydraulics, mathematical physics, mechanics, physics, technical physics, theory of elasticity sections)		
		Proceedings of the Academy of Sciences of the USSR, Applied Physics Sections (does not include mathematical physics or physics sections)	American Institute of Physics	106 1 1956
		Wood Processing Industry		
		Telecommunications	Consultants Bureau	106- 1 1956- 1957
		Entomological Review	Timber Development Association (London)	9 1959
		Pharmacology and Toxicology	Massachusetts Institute of Technology*	1 1957
		Physics of Metals and Metallography	American Institute of Biological Sciences	38 1 1959
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		Measurement Techniques	The Geochemical Society	1 1958
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			Instrument Society of America	1 1959
			Consultants Bureau	1 1952

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		Kinetika i kataliz	Consultants Bureau	1	1960
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		Metallurg	Acta Metallurgica	1	1957
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		Priboirostroenie	British Scientific Instrument Research Association	1	1959
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		Prikladnaya matematika i mekhanika	American Society of Mechanical Engineers	1	1958
		(see Priboiry i tekhn. éks.)			
		Problemy Severa	National Research Council of Canada	1	1957
		Radiotekhnika	Massachusetts Institute of Technology*	12	1957
		Radiotekhnika i élektronika	Massachusetts Institute of Technology*	2	1957
		Stanki i instrument	Production Engineering Research Assoc.	1	1959
		Stal'	Iron and Steel Institute	13	1956
		Steklo i keramika	Consultants Bureau	1	1956
		Svarochnoe proizvodstvo	British Welding Research Association	4	1959
		Teoriya veroyatnostei i ee primeneniye	Society for Industrial and Applied Mathematics	1	1956
		Tsvet. Metall	Primary Sources	66	1960
		Uspekhi fizicheskikh Nauk	American Institute of Physics	1	1958
		Uspekhi khimii	The Chemical Society (London)	1	1960
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		(see UFN)			
		(see UKh)			
		(see UMN)			
		Uspekhi sovremennoi biologii	Oliver and Boyd	48	1959
		Vestnik mashinostroeniya	Production Engineering Research Assoc.	4	1959
		Voprosy gematologii i perelivaniya krovi	National Institutes of Health*	1	1957
		Voprosy onkologii	National Institutes of Health*	1	1957
		Voprosy virusologii	National Institutes of Health*	1	1957
		Zavodskaya laboratoriya	Instrument Society of America	25	1959
		Zhurnal analiticheskoi khimii	Consultants Bureau	7	1952
		Zhurnal éksperimentalnoi i teoreticheskoi fiziki	American Institute of Physics	28	1955
		Zhurnal fizicheskoi khimii	The Chemical Society (London)	7	1959
		Zhurnal mikrobiologii, épidemiologii i immunobiologii	National Institutes of Health*	1	1957
		Zhurnal neorganicheskoi khimii	The Chemical Society (London)	1	1959
		Zhurnal obshchei khimii	Consultants Bureau	19	1949
		Zhurnal prikladnoi khimii	Consultants Bureau	23	1950
		Zhurnal strukturalnoi khimii	Consultants Bureau	1	1960
		Zhurnal strukturalnoi khimii	American Institute of Physics	26	1956
		Zhurnal tekhnicheskoi fiziki	National Institutes of Health*	1	1958
		Zhurnal vysshei nervnoi deyatel'nosti (im. I. P. Pavlova)			

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SIGNIFICANCE OF ABBREVIATIONS MOST FREQUENTLY
ENCOUNTERED IN SOVIET PERIODICALS

FIAN	Phys. Inst. Acad. Sci. USSR
GDI	Water Power Inst.
GITI	State Sci. -Tech. Press
GITTL	State Tech. and Theor. Lit. Press
GONTI	State United Sci. -Tech. Press
Gosenergoizdat	State Power Press
Goskhimizdat	State Chem. Press
GOST	All-Union State Standard
GTTI	State Tech. and Theor. Lit. Press
IL	Foreign Lit. Press
ISN (Izd. Sov. Nauk)	Soviet Science Press
Izd. AN SSSR	Acad. Sci. USSR Press
Izd. MGU	Moscow State Univ. Press
LEIIZhT	Leningrad Power Inst. of Railroad Engineering
LET	Leningrad Elec. Engr. School
LETI	Leningrad Electrotechnical Inst.
LETIIZhT	Leningrad Electrical Engineering Research Inst. of Railroad Engr.
Mashgiz	State Sci. -Tech. Press for Machine Construction Lit.
MEP	Ministry of Electrical Industry
MES	Ministry of Electrical Power Plants
MESEP	Ministry of Electrical Power Plants and the Electrical Industry
MGU	Moscow State Univ.
MKhTI	Moscow Inst. Chem. Tech.
MOPI	Moscow Regional Pedagogical Inst.
MSP	Ministry of Industrial Construction
NII ZVUKSZAPIOI	Scientific Research Inst. of Sound Recording
NIKFI	Sci. Inst. of Modern Motion Picture Photography
ONTI	United Sci. - Tech. Press
OTI	Division of Technical Information
OTN	Div. Tech. Sci.
Stroizdat	Construction Press
TOE	Association of Power Engineers
TsKTI	Central Research Inst. for Boilers and Turbines
TsNIEL	Central Scientific Research Elec. Engr. Lab.
TsNIEL -MES	Central Scientific Research Elec. Engr. Lab. - Ministry of Electric Power Plants
TsVTI	Central Office of Economic Information
UF	Ural Branch
VIESKh	All-Union Inst. of Rural Elec. Power Stations
VNIIM	All-Union Scientific Research Inst. of Metrology
VNIIZhDT	All-Union Scientific Research Inst. of Railroad Engineering
VTI	All-Union Thermotech. Inst.
VZEI	All-Union Power Correspondence Inst.

NOTE: Abbreviations not on this list and not explained in the translation have been transliterated, no further information about their significance being available to us. -Publisher.



